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SPECIAL ARTICLE.

VASCULAR TENSION IN CHRONIC ILLNESS.

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Thirty years ago, the study of disease of the vascular system scarcely did more than cover the lesions of the valves of the heart, a consideration of gross lesions in its muscle, and a brief reference to the grave changes found in the bloodvessels when they were affected by marked fibrosis or atheromatous change, or one plugged by emboli or thrombi. Little attention was paid to the changes in the finer arterioles except when these changes were well developed, and nothing was said of the functional state of the arterial system in its relation to circulatory disorders. Nearly all the treatment advised was directed to the heart itself, and the importance of the vasomotor system as a factor in disease was almost ignored. At the present time, however, medical men in general have come to recognize the fact that a vascular system intact, both functionally and anatomically, is essential not only to the health of the body in general but of the heart in particular. Not only may serious consequences to the heart follow the development of arteriocapillary fibrosis, but, in addition, mere spasmodic contractions of the arterioles, to a degree in excess of the normal, may be disastrous in acute conditions; and the antithesis of spasmodic contraction, namely, vascular relaxation, may result in speedy death, either by bleeding the man into his own vessels, or by causing cardiac exhaustion in the endeavor of this organ to fill the relaxed vessels. The object

of these remarks, therefore, is to emphasize the importance of studying the vascular state and the degree of the blood pressure in respect to the diagnosis, prognosis, and treatment in several states of disease, and they are called forth because a fairly large experience has convinced me that many medical men are still impressed with the idea that a tired heart should be stimulated to greater effort when in reality it should be given as much rest as possible by diminishing its burden. I believe that this is one of the grave mistakes in modern diagnosis and treatment.

If we take, as an example, any one of the grave infectious diseases characterized by toxæmia, we find that the heart fails, if it fails at all, as a result of poisoning of its muscle or disorder of its nerve supply arising from the same cause, and against this muscle poison our stimulants do not act as true antagonists. The longer I study these cases the more I am impressed with the fact that active cardiac stimulation is often more harmful than advantageous, unless we can resort to measures designed to diminish the toxæmia, and by decreasing the toxæmia permit the heart to do its work. As a matter of fact, the vascular system in these cases shows, if it be carefully studied, that it is much more responsible for the circulatory depression which is present than is the heart, and an examination of the patient's vessels will reveal the fact that they are widely dilated, and of the heart that it is working more actively and more forcibly than in health in an endeavor to fill the relaxed arterioles. The patient's death is doubtless imminent because of circulatory failure, but the heart, in a considerable portion of cases fails only when it is tired out in the vain attempt just alluded to. To use a simile which I have used before, the heart under these circumstances may be compared to a locomotive on a slippery track. It fails to push its load not because it is weak, but because it finds no resistance on the rails. The more the locomotive is stimulated to increased endeavor by opening the throttle wider and wider, the more it shakes itself to pieces, the more it expends its energy, and it gains nothing. The heart is designed to beat against a very considerable arterial tension, just as the locomotive is required to work against a given load; but here the simile ceases, for the locomotive gathers no strength from the friction or resistance of the rails and train, whereas the heart depends absolutely for its existence upon such resistance, because if the arterial pressure falls the heart muscle gets less blood through its coronary arteries and through the vessels of Thebeseus. A very low tension, therefore, means an increased but worthless expenditure of energy and a decreased nutritive supply to the overworked muscle fibres. Fortunately most of the drugs commonly used by physicians under these conditions are, as a matter of fact, both cardiac and vascular stimulants, and so the patient gets the needed vascular effect.

It is quite remarkable how competent the heart is to attend

to its functions if the physician is able to overcome vascular relaxation. There are only three drugs which have seemed to me to be competent for this purpose, namely, atropine, adrenalin, and digitalis, and I have placed them in their order of usefulness: for atropine by contracting the great vascular areas of the abdomen raises arterial pressure everywhere and, according to Hedborn, dilates the coronary vessels, and so increases the cardiac blood supply without directly stimulating the heart muscle to increased endeavor.

Two states of deleterious high tension are also overlooked, namely, the high tension of acute illness and the high tension of prolonged nervous and mental stress. The high tension of cases of acute illness rarely approaches the high tension characteristic of arteriocapillary fibrosis for obvious reasons, and so is not so readily recognized by the physician who is careless of this aspect of his patient's case; but, nevertheless, it is important for us to recall that its modification is much more advantageous than the very popular efforts to reduce fever, which is an associated symptom of comparatively little importance. Whether the high tension occurs early in the illness or at a later stage, vascular relaxants, which are not cardiac depressants, will save the heart from the expenditure of a large amount of unnecessary effort, and thereby enable it to withstand calls upon its reserve energy.

I wish to call attention to only two more points in regard to this matter of high arterial tension in acute disease, namely, that physicians often, in their terror of cardiac failure, give circulatory stimulants when a comparison of the patient's pulse force and tension with that in their own vessels will show that their own circulation, although normal, is at a lower ebb than the patient's, and by giving stimulants when fever is already causing excessive cardiac and arterial activity, they place themselves in the position of the man who beat his horse into a run for fear he would give out before he got to the end of the journey.

The second point is that our forefathers, while they were empirics, were often more skilful in these cases than many so-called scientific moderns, for they gave vascular relaxants in the form of spirit of nitrous ether, which is, after all, like nitroglycerin in its effects, and Dover's powder, which produces similar influences.

The subject of arterial spasm or fibrosis in its relation to cardiac failure, in those who are subjected to mental strain, is too large a field to be discussed at this time, although it is more important than any of the fields already spoken of. I have recently discussed it at length elsewhere.[1]

To express the matter briefly we meet with three classes of cases of high arterial tension of this type: (1) Those in which persistently high tension is a result of spasm due to prolonged nervous stress

[1] Therapeutic Gazette, December, 1905.

combined with certain abuses as to habits of life, food, and drink. (2) Those in which tension is high because in addition to spasm there is gradually developing, or has already developed, fibroid changes in the vessels. (3) Cases in which, after a prolonged period of high tension, there, more or less suddenly, develops persistent low tension in which the arteries are relaxed and distended, so that, to some degree, they resemble veins in their calibre and compressibility.

In the first and second classes rest in bed, with massage and the nitrites, is essential. In the third class the rest in bed is needed also, but vascular stimulants are required. In all these cases the iodides are valuable. If the high tension is due chiefly to spasm, nitroglycerin will do good for obvious reasons, but it will fail to a great extent if the condition is due to fibrosis. This is an important therapeutic point, showing that the physician can expect nitroglycerin to reduce only that part of the hypertension which is due to spasm and not that part due to fibroid change. The latter stage is largely beyond the influence of medicinal agents, unless it be the iodides. On the other hand, the combined effect of rest, massage, and iodides will often, even when fibrosis is well developed, not only produce excellent results, in that the state of a tired heart is improved, but also result in a marked diminution of arterial tension, partly by a cardiac and partly by a vascular influence.

There is still another class of cases in which high arterial tension is present which deserves notice, namely, those persons of somewhat advanced years who have gradually developed a high tension of moderate degree, and to this tension the heart, vessels, and tissues have become adjusted, so that it has become a "standard tension," so to speak. With the onset of an acute illness the physician may find this standard tension somewhat exaggerated, and, impressed with the general principle that a high tension is evil, he proceeds to lower it to normal instead of to the new normal standard of the individual under observation. This is usually unwise, and each patient must be studied carefully in this respect.

Finally, let me sum up the points which I am desirous of presenting to the clinician:

1. Cardiovascular stimulants are often given when vascular relaxants are really needed.

2. More attention to the protection of the heart from unnecessary labor is advisable.

3. If the physician will direct his treatment to the vessels the heart will often be able to care for itself.

4. Do not stimulate a heart to increased effort when the real object is to decrease its burden and to diminish the toxæmia which is destroying its function.

ORIGINAL ARTICLES.

THE THERAPEUTIC USE OF TUBERCULIN COMBINED WITH SANITARIUM TREATMENT OF TUBERCULOSIS.[1]

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The wild enthusiasm which greeted Koch's announcement in 1890 of his discovery of tuberculin and his claims for its diagnostic and therapeutic possibilities was, as you know, very soon followed by bitter denunciations of the proposed method of treatment, and even of the distinguished scientist himself. Tuberculin was soon abandoned, and for a long time was considered as so dangerous that its use was looked upon as akin to malpractice. A few physicians, however, both here and abroad, continued the study of its careful application to cases of pulmonary tuberculosis, and of late more frequent publications on this subject point to renewed interest in the employment of some sort of vaccine as an immunizing agent in this disease.

So general and bitter was the condemnation of tuberculin that between 1891 and 1900 it was with the utmost difficulty that I could persuade a few patients at the Sanitarium each year to take the treatment while in the institution. As I have, however, used tuberculin injections continuously, though at times in a limited number of cases only, at the Sanitarium ever since 1890, I have thought that a summary of the impressions I have gained from my experience might prove of interest. Dr. Lawrason Brown has already published a detailed report of the cases treated at the Adirondack Cottage Sanitarium up to 1903. I shall not attempt to review the extensive literature of the subject, to discuss lengthy statistics bearing on the comparative results, or to go into a detailed history of cases, but will merely confine myself, as far as possible, to my own experiences, and briefly state my impressions of this method of treatment.

As a diagnostic agent, the tuberculin test has been used at the Sanitarium occasionally for the past fifteen years. So far as its danger is concerned, my observation has been that when given according to the well-recognized rules which alone make its administration justifiable I have never known any ill effects follow the test beyond occasionally a somewhat severe or prolonged reaction, except possibly in three cases, which were somewhat unpleasant experiences. One occurred in the practice of another physician, and two were at the Sanitarium. In the first case there was constitutional impair-

[1] Read at the meeting of the National Association for the Study and Prevention of Tuberculosis, Washington, D. C., May 17 and 18, 1906.

ment, without any marked physical signs, and a test injection of old tuberculin resulted in a moderate reaction, which subsided, but was soon followed by an aggravation of all the symptoms, and I believe the patient ultimately did badly. The other two cases were at the Sanitarium. In one case, a slight hemorrhage followed the first reaction two weeks after its subsidence, but there was no other ill effect. In the other, after four days of normal temperature following the first reaction, blood-spitting occurred, and an exacerbation of all the symptoms, with marked fever, followed and continued for some time. Whether these occurrences were merely coincidences, or were due directly or indirectly to the tuberculin, it is difficult to be certain.

Picket, who recently injected 929 patients, in order to confirm a diagnosis of pulmonary tuberculosis when the bacillus was absent, saw quite prolonged disturbance of the patient's condition follow in three cases, while in twenty the reactions were "more violent than desirable." At the Sanitarium the test has been of great value in helping to reach a conclusion as to the absence or presence of tuberculosis, especially in closed tuberculosis, or when the tuberculous nature of a pulmonary lesion was in doubt; a conclusion which, in the great majority of cases, has proved to be correct and of inestimable value to the patient.

The tuberculin test should never be resorted to until the physician has failed to reach a conclusion after a careful application of the clinical methods of diagnosis. As our skill in the detection of closed tuberculosis increases, it may be necessary to use the test only in exceptional cases, as the reactions at best are sometimes an unpleasant experience for the patient. On the other hand, the more we realize how really curable closed tuberculosis is the more valuable becomes a method which reveals its presence when all other clinical means fail.

I have persisted in the study of tuberculin treatment at the Sanitarium, not on account of any immediate brilliant results noticed in its application, although I saw enough of its effects to encourage me to persevere in its use; but principally, in spite of the popular clamor against it, because it is based on a certain degree of success demonstrable in animals by the experimental method, and because the production of artificial immunity by the specific poison of a disease is the line along which success has already been attained, and is being attained, in other infectious diseases.

The experimental evidence on which tuberculin treatment is based is not as complete or satisfactory as one would wish. Koch gave no details of the method by which he attempted to immunize and cure guinea-pigs with old tuberculin, T. R., or Bacillen Emulsion, but merely states that they can be rendered resistant to subsequent inoculations, and that when treated by these products, their lesions show marked evidence of fibrosis. His associates published details

of experiments, but the results, although encouraging, did not show complete cure or immunity. Other observers have reported a varying degree of success in the immunization of small animals, and in their treatment by bacillary products. Broden,[1] perhaps, gives one of the most detailed descriptions of the good results which he obtained in dogs injected with the filtrate of liquid cultures, both before and after intraperitoneal inoculation, and demonstrates the curative influence of tuberculin as shown by a comparative microscopic study of the lesions of the treated and the untreated animals, as well as by the survival of the former and the death of the latter. Pathological observations bearing on the microscopic appearances of the lesions of patients who have been treated successfully with tuberculin, and have died of other causes, would be of great value at present.

The most convincing evidence of the favorable results of tuberculin that my own experimental work has shown me, I obtained and published as early as 1892. By treating tuberculous iritis in the rabbit's eye by subcutaneous injections of the unheated filtrate of bouillon cultures of the tubercle bacillus, a retrogression of the lesion and an apparent healing gradually took place, which, however, ultimately relapsed somewhat, though very slowly. I have found that guinea-pigs and rabbits previously injected with dead tubercle bacilli live on an average somewhat longer than control animals when subsequently inoculated. The beneficial influence of treatment of small animals with various products of the tubercle bacillus, however, is demonstrated, not by the cure of a progressive generalized tuberculosis in them, for this does not occur; but by the evident tendency to healing shown in localized tuberculosis, and in the more chronic course of the disease in the treated as compared with the untreated animals.

The immunity obtained by non-living products of the tubercle bacillus, however, is only relative, and is not to be compared to that which I have been able to produce by preventive inoculations of living attenuated cultures. Behring's experiments of cattle immunization thus far published show the same thing, namely, that he obtained no solid immunity in cows with various *non-living* tuberculous products, but that he achieved success and produced a solid immunity by previous inoculations of living human cultures. All these experiments establish for tuberculosis, by unquestionable evidence, the principle of artificial immunization, hitherto looked upon as impossible of achievement.

Animal experiments, therefore, on which tuberculin treatment in man is based, show that tuberculin immunity is not identical with immunity to tuberculosis, for it does not protect animals abso-

[1] Recherches sur l'histogenese du Tubercle et l'action curative de la Tuberculine. Archiv. de Médecine Experimentale, January, 1899.

lutely against inoculation tuberculosis, nor materially retard the course of generalized tuberculosis. It would seem that contact between the living bacillus, or the product of the living bacillus, and the cell, is necessary to the production of a solid and lasting immunity, for up to the present this immunity to tuberculosis or to other bacterial diseases has been accomplished in animals only by protective inoculations of a living germ. Behring, however, in his recent announcement claims to have discovered a successful method of immunization for cattle without the use of living bacilli.

Nevertheless, tuberculin immunization, even in the most susceptible animals, undoubtedly prolongs life somewhat, retards the development of the disease in its earlier stages, and produces changes in the lesions which demonstrate an attempt at healing, and this, in localized tuberculosis, may be equivalent to a more or less complete cure. The limitations of tuberculin in the treatment of experimental tuberculosis in animals should, therefore, be borne in mind in judging the results of tuberculin treatment in human beings. Why should we expect it to do more for man than it can accomplish in animals?

To what extent, if any, does tuberculin immunization induced in man favorably influence the course of human tuberculosis? From the renewed interest in this form of treatment it seems that the claims of this method are soon to be thoroughly and dispassionately settled.

Most of the proposed tuberculins have been tested at the Sanitarium. The first used was Koch's original tuberculin. Later, after the publication of Hunter's work in 1891, I made his Modification B., myself, from the filtrate of liquid cultures. The albumoses contained in the unheated culture medium, having been precipitated with ammonium sulphate, were taken up in distilled water and dialysed, Hunter claiming more local and less general reaction from this product. This preparation was used at the Sanitarium for a time. In 1898, Buchner's Tuberculo-plasmin, and in 1900, Landmann's Tuberculol, were both tried, as well as Koch's T. R., and since 1901, Koch's Bacillen Emulsion has been principally used; but Koch's three tuberculins have been most generally employed.

The use of these preparations gave rise to symptoms which were nearly identical, and are the well-known ones of tuberculin reaction. It has been impossible to reach any conclusion as to the relative therapeutic value of these different preparations. Koch's T. R. and Bacillen Emulsion seem to be more uncertain in their action, and to produce more frequently strong and unexpected reactions. This is a serious objection to their use, as occasionally unexpected and pronounced reactions occur, even if the dose is increased with the utmost caution. The reason for this undoubtedly, to a great extent at least, lies in the fact that they are mostly emulsions and not solutions; that absorption of such a suspension is much

more difficult and uncertain than that of a readily soluble toxin; and that unless great care is exercised in thoroughly shaking the bottles, and in drawing from the centre of the liquid rather than the top or bottom, the dilutions made will contain very varying amounts of the suspended but undissolved bacterial substance.

Reasoning from analogy and from what we know of artificial immunization in other bacterial diseases, tuberculins in the preparation of which no heat has been applied are likely to be the most efficient. Koch's Bacillen Emulsion, and the filtrate of ripe cultures as used by Denys, meet this requirement. The first contains all the toxins and endotoxins to be found in the bodies of crushed tuberle bacilli; the second, the toxins and any other substances which may be produced by the growth of the bacilli, or dissolved from their disintegrating bodies in a liquid medium, and both are entirely unaltered by heat.

It is possible that the chemical researches of de Schweinitz, Levene, Behring, Ruppel, and others, exhaustive as they have been, may be carried still further, and that organic chemistry may yet produce a more efficient tuberculin by the elimination of certain substances which are injurious, and the retention of others which are immunizing. But Koch's long and careful work in this direction is suggestive, for after prolonged investigations which resulted in his T. R. tuberculin, he has more recently put forth his Bacillen Emulsion, which is merely a suspension of crushed tubercle bacilli, and contains entire and unaltered all the toxins contained in the bodies of the bacilli. Behring's announcement, on the other hand, is full of encouragement. His T. C. is a toxin which differs from Koch's T. R. principally in its freedom from the waxy elements contained in the bodies of the bacilli, and it is possible it may prove to be a more efficient tuberculin than any we now possess. From what we may infer from Behring's guarded and enigmatical utterance, he has gone even further, and it would seem that he has succeeded in transforming by contact with the living cell his T. C., which is a toxin, into his "Tuberculase," which is an immunizing and curative substance capable of immediate absorption by the cells of susceptible animals and man, and thus producing the desired immunity. Dr. Theobald Smith, as a result of his recent studies on animals, suggests virulent uncrushed tubercle bacilli, killed by moderate heat, as the best vaccine to be tried in attempts at immunizing human beings.

With a few exceptions, in which, soon after Koch's discovery, tuberculin was given as a last resort to far advanced patients who begged to be treated, the patients selected for treatment at the Sanitorium have belonged to the incipient and advanced class, who were mostly apyretic, or whose temperature at irregular intervals reached only from 99.5° to 100°, and whose general nutrition was good. The acute types, or those suffering from marked febrile

remission or hectic fever, were excluded. Patients running a continuous temperature, even if not above 100°, with little to be heard in the lungs, but with rapid pulse, emaciation, debility, and cachexia, pointing to scattered miliary tuberculosis, were also excluded. Elsassar, Denys, and others advocate the use of tuberculin injections even in acute febrile cases, but I have had no experience with such cases.

For a long time the tendency was to choose as favorable cases as possible, from both the incipient and advanced classes, for treatment; but little by little less favorable cases were selected, and during later years those whose condition seemed to be at a standstill, and to have but little chance of arresting their disease by the hygienic and open-air method alone, have been frequently treated. It cannot be denied, however, that the desire to select, from whatever class, patients whose nutrition was good, prevailed to a greater or less extent, and must have somewhat influenced the results.

The first impression which the physician receives who begins to make use of tuberculin is a most profound respect for the tremendous potency of this toxin. A toxic substance which, in so infinitesimal a dose as the one five-thousandth of a milligram of the solid substance contained in Koch's Bacillen Emulsion, may produce typical and marked constitutional disturbance in the tuberculous individual, is certainly not to be used heedlessly, and is potent for evil if carelessly administered. I would not urge any physician who prizes his peace of mind to embark on the treatment of tuberculosis by this method unless he is prepared to begin with minute doses and increase with the utmost caution. He will also soon be made to feel the deep-rooted prejudice which exists, both in the profession and laity, against tuberculin treatment, and he must be prepared to meet criticism and blame for all the exacerbations and complications which naturally develop in the course of the disease, and which are invariably attributed not to the disease but to the treatment; while coincidences will occur occasionally which make his position indefensible, and which he must be prepared to face as best he can. I have seen tuberculous meningitis, hæmoptysis, and uncontrollable pyrexia, all ending fatally, occur in patients who were about to take tuberculin, but for some reason or other did not take it.

The method of administration is of the greatest importance, and has varied as time passed. At first little attempt was made to avoid reactions, which were advised by Koch, and which he still seems to consider as necessary to success in this form of immunization, for in his last paper on Bacillen Emulsion he says: "One increases the dose very rapidly in order to obtain very pronounced reactions, with elevations of temperatures of 1.5° to 2° C. As soon as a strong enough reaction is obtained, the intervals must be lengthened to from six to eight days or more."

From my own experience with tuberculin I have formed the impression not only that fever reactions are not necessary to obtain good results, but that although occasional moderate reactions are unavoidable and apparently do no harm, every effort should be made to avoid them. If frequent and violent, they have a bad effect on the patient's general condition, and are by no means free from danger, as was shown during the early history of tuberculin treatment, the danger being the production of continuous fever, cachexia, and increased activity in the disease.

If we abandon the view that fever reactions are necessary to obtain results, and look upon them as the result of overstimulation; if we accept as a working theory that any curative influence of tuberculin is due not only to a local reaction of the lesion but also to a stimulation of the body cells by the injected toxins—a stimulation which results in the production of some sort of anti-body by these cells, as well as possibly an increased activity of the phagocytes—the best method of treatment would undoubtedly be to continue this stimulation by minute and very gradually increased doses for as long a period of time as possible. Whatever reactions unavoidably occur are only to be considered as indicating that the limit of the patient's capacity for responding, by the formation of antitoxic or antibacterial substances, to the stimulus of the injections has been exceeded.

We must divest our minds of the impression that because small doses produce no immediate apparent effect they are, therefore, ineffectual, for we have ample evidence to the contrary. A minute amount of tuberculin, which produces no rise of temperature when injected in rabbits with tuberculous iritis, nevertheless is capable of bringing about a very appreciable local reaction and leukocytosis. The same occurs in tuberculous nodes and lupus, and the work of Wright and Douglas proves that minute doses, and a very gradual increase, are met by a very appreciable and easily demonstrable response of the defensive resources of the living organism.

The best method has seemed to me to begin with very minute doses—1/10,000 or even 1/20,000 of a milligram of solid substance Koch's Bacillen Emulsion, or a 1/100 of a milligram of old tuberculin—and increase so gradually and at such intervals as to carry the patient to full doses with as little disturbance as possible; and by taking sufficient time, most patients can be taken through the entire treatment with but occasional and moderate reactions. At the slightest evidence of intolerance, as manifested not only by the patient's temperature, but by his symptoms, by marked irritation at the site of injection, or depreciation of his general condition, the intervals between the injections should be lengthened and the dose diminished for a time. Care should be taken never to inject after a reaction until all effects of the previous reaction, both on

the patient's temperature and general condition, have entirely passed away. I have also formed the impression that the treatment should be extended over as long a time as is needed to avoid reactions, no matter how long that may be, and that time is an important element in obtaining the best results. Six months of treatment is almost always necessary, and a year or more would be better in many cases.

The patient, while taking the injections, should show no depression of general health, and should have no fever above his usual temperature range, except it be occasionally for the forty-eight hours following an increase of dose; if this occurs the treatment should be discontinued, and only resumed when he has recovered his normal condition. If full doses, that is, 1 c.c. of old tuberculin, or 5 milligrams of solid substance Bacillen Emulsion, can be reached without violent reactions and without depreciation of the general health, *but not otherwise*, the injections should continue until one full dose has been given; but the intervals should be lengthened gradually as the higher doses are reached, and extended to two weeks between the last two or three injections. The physician must, of course, individualize, and be guided throughout the treatment, and in his judgment *as to the dosage to which it is to be carried*, entirely by its effect on the patient; and on his watchfulness and skill will greatly depend the safety of the patient and the degree of success attained.

I quite agree with Denys that the principal faults in treatment—faults which may lead to failure, and even seriously endanger the patient's chance of recovery—are:

Beginning the treatment with too large amounts; raising the dose too rapidly or at too short intervals; injecting again before all effects of a reaction, both constitutional and local, have passed away; increasing the dose after a reaction has occurred; neglecting to consider malaise, headache, loss of appetite, and increased cough, as evidences that the limit of the patient's tolerance has been reached, and calls for an interval of rest and a reduction of the dose. The physician who disregards as of no importance an increase of a minute fraction of a milligram of tuberculin, or a rise of a few tenths of a degree of temperature, will meet with disappointment and disaster in the application of tuberculin treatment. I have become convinced that any danger there may be of aggravating the patient's condition by tuberculin treatment lies principally, if not wholly, in its faulty or reckless administration.

Tuberculin immunity does not last indefinitely, and it may be well for the patient to take another course of treatment in four to six months if any symptoms should reappear; but with a very few exceptions the patients at the Sanitarium have taken but one course of injections.

The serum agglutination method, as proposed by Koch, has not

been found reliable either as a guide to dosage or as an indication to the degree of immunization produced by tuberculin.

The most interesting work of Wright and Douglas on the production of opsonins in the blood, the presence of a positive and negative phase in artificial immunization, and finally the application of the opsonic index as an accurate guide in regulating the doses of vaccine and intervals between injections, is a brilliant contribution to our knowledge of the mechanism of artificial immunization, and a striking attempt at the practical application of exact laboratory methods to the treatment of disease. It is to be regretted, however, that even if the deductions Dr. Wright draws as to the necessity of being guided by the rise and fall of the opsonic index, and even if the accuracy of his method of determining it should be confirmed, the degree of skill required in carrying out such delicate technique and the time and work necessary in the determination of the opsonic index, make it generally impractical of application to the treatment of disease in a large number of patients. Besides, as Elsassar remarks in regard to the agglutination method, the patients object to periodical phlebotomies; the reactions are quite enough for them.

The immediate results of tuberculin treatment are not very striking, and up to the time of discharge (generally six months), when patients, treated and untreated, who were classified alike on admission, are compared, there is little difference to be noted in their condition, as the majority, especially in the incipient class, whether treated or not, show more or less marked improvement in symptoms and general condition. It is rather when studying the effect of the injections in patients somewhat more advanced in the disease that one notes occasionally unusually rapid and unexpected improvement, and that the preponderance of improvement seems to be in favor of the patients who have taken tuberculin.

The physical signs in tuberculin-treated cases may appear to grow worse, and rales develop where they were not heard at first, while the expectoration increases; but if no strong reactions have occurred this is not marked, and everything in the chest soon returns to its usual condition and the expectoration lessens if the doses are not pushed too rapidly. Even the disappearance of bacilli is often not much more marked in the treated than in the untreated incipient cases up to the time of discharge, but in advanced cases the comparison with similar untreated cases is in favor of the treated.

I nevertheless have formed the impression that the use of tuberculin brings about somewhat better results than can be obtained by sanitarium methods alone, even up to the time of discharge. The statistical evidence I have been able to gather, and which seems to confirm these impressions, was made for the Sanitarium records at my request by Mr. E. S. Pope, an expert mathematician, to whom

my acknowledgments are due; and I present the evidence of his exhaustive study in as condensed form as possible.

The influence of tuberculin injections on the disappearance of bacilli from the expectoration, when the entire number of treated and untreated patients at the Sanitarium is considered, is as follows:

Of those who had bacilli in the incipient class, 64 per cent. of the untreated and 67 per cent. of the treated lost them; of those classified as advanced on admission, 44 per cent. of the treated lost them, and 24 per cent. of the untreated.

In regard to the results at discharge, Mr. Pope writes: In some years there have been few, and in other years many tuberculin cases. The standards of classification have varied from time to time. Now if there were a large number of treated cases in a year of low standard, the tendency would be to make the total results for tuberculin unduly good. If these conditions were reversed, the opposite result would be obtained. By reducing (or increasing) the numbers of treated and untreated cases to one hundred in each class, in each year, this difficulty is avoided. The correct way to do this is not to select the cases, but to multiply or divide the actual numbers in each class for each year so as to make them equal to one hundred. This applies to the following table:

Comparison of 185 *Patients Treated and* 864 *Untreated.* There have been excluded all who stayed less than ninety days, and all who did not have tubercle bacilli on admission.

For the reasons given above, the following percentages have been calculated on the basis of an equal number of treated and untreated patients in each year.

The results at the time of discharge were as follows:

	Incipient.			Advanced.		
	Apparently cured.	Disease arrested.	Active.	Apparently cured.	Disease arrested.	Active.
Treated . . .	56 p. c.	34 p. c.	10 p. c.	27 p. c.	55 p. c.	18 p. c.
Untreated . .	50 p. c.	38 p. c.	11 p. c.	6 p. c.	51 p. c.	43 p. c.

In considering these figures we are at once struck with the fact that the advanced cases, both so far as the loss of bacilli and the condition at discharge are concerned, seem to derive proportionately much more benefit from the treatment than the incipient cases. I will refer to this later. You all know how unsatisfactory and unconvincing conclusions based solely on statistics relating to sputum examinations and classification of results can be. The uncertainties of sputum examinations, unless several examinations extending over considerable time are made, and the personal equation of the physician cannot be excluded as influencing the classification of a patient at discharge, and are among the most obvious and misleading sources of error in such statistics.

The study of the post-discharge mortality, however, would seem to promise much more satisfactory and conclusive evidence. Through carelessness we may all fail to find bacilli though they be present; and we may all differ as to whether a patient at discharge is "apparently cured" or the disease "arrested;" but there can be no doubt as to whether the patient be living or dead. Besides, the object of sanitarium treatment is not the condition of the patient at discharge but the prolongation of his life, and time must ever be the crucial test of any treatment. Mr. Pope has condensed for me his canvass of the post-discharge mortality, which bears on 135 treated and 690 untreated patients discharged in the past fifteen years from the institution.

Comparison of 135 *Patients Treated and* 690 *Untreated.* Equal numbers of treated and untreated patients in each year are considered; all patients who stayed less than three months, all who left the Sanitarium less than one year ago, and all untraced patients have been excluded.

	Incipient.		Advanced.	
	Living.	Dead.	Living.	Dead.
Tuberculin treated	79 p. c.	21 p. c.	61 p. c.	39 p. c.
Untreated	63 p. c.	37 p. c.	36 p. c.	64 p. c.

From these figures we gather that 18 per cent. more of treated incipient cases are living than of untreated, while 25 per cent. more of advanced cases who received tuberculin are living than of those who did not. The value of such comparative statistics, however, depends entirely on two things: the accuracy of the figures, and the explanation of the results they represent. As to the accuracy of the figures I have little or no doubt, but I regret that I am by no means so certain of their exact value as demonstrating the curative influence of tuberculin. The question is, Are the favorable results which these figures seem to indicate due solely to tuberculin treatment or to other factors?

The only sources of error with which I am acquainted are the influence of the selection of cases, and the fact that the treated remained often much longer in the institution, in order to complete their treatment, than the untreated.

It is impossible to estimate how much the selection of cases has influenced the results, and the more favorable comparative results obtained in the advanced class may be interpreted in two ways, and does not help us much in reaching a correct conclusion. Any specific curative influence of tuberculin would be shown more markedly by prolongation of life in the advanced class, in which the disease was tending toward a fatal termination, than in the incipient class, in which the disease in the majority of cases inclined to arrest and cure without the aid of any specific treatment. On the other hand, selection of cases would have more influence on the results in the

advanced than in the incipient class, because the advanced class is much more comprehensive than the incipient, and there is often as much difference between favorable advanced and unfavorable advanced cases as between incipient and advanced.

Having stated the facts, I must, therefore, leave the interpretation of the figures to the individual judgment of those who may be interested in them. Many years ago, in spite of the general denunciation of tuberculin, and long before I knew anything about the statistical evidence, I had formed the opinion that tuberculin, when carefully administered, had within certain limits a favorable influence on the course of the disease, and that the results of sanitarium treatment could be improved and made more permanent in many cases by its application. As years have passed I have seen no reason to change this opinion, which the figures I have just quoted, however they may be interpreted, do not at any rate tend to contradict.

REVIEW OF THE WORK UPON THE OPSONIC INDEX (WRIGHT AND DOUGLAS) IN TUBERCULOSIS.[1]

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Historical. Ehrlich's theory of immunity developed the conception that before a bacterial intoxication can take place a definite chemical union must exist between the cells of the affected individual and the toxins of the invading microbe. Wright named the various toxins "tropins," because they are substances which turn toward a cell. He calls the toxin of tetanus a "neurotropin," because it combines with the nerve cells. Such a union between tropins and cells calls forth a reaction upon the part of the infected individual to produce so-called "antitropins," which are protective substances. Many kinds of antitropins exist—antitoxins, agglutinins, precipitins, lysins, opsonins, etc. Wright believes that a sufficient amount of such substances within the body is responsible for the existence of natural immunity, and that their elaboration is capable of conferring an artificial immunity. The art of

[1] Read in part by one of us at the meeting of the National Association for the Study and Prevention of Tuberculosis, Washington, D. C., June 17 and 18, 1906.

immunization consists in developing in the animal in question the best conditions for a maximal antitropin formation.

Metchnikoff's patient investigations into the secrets of immunity are based upon his fundamental conception that the existence or cultivation of immunity depends upon the digestive action of certain cells of the body—"phagocytes." Ehrlich's hypothesis and recent contributions to the study of immunity, however, have compelled Metchnikoff to include under the term "phagocyte" a number of cells of different origin. Although he has been obliged to acknowledge the existence of antitropins in the fluids of the body, he has persisted so valiantly with his original conception that he now holds that these bodies are derived from some chemical process, a sort of fermentation going on inside the phagocytes.

At the other extreme the advocates of the humoral theory believe that phagocytosis is a secondary process, a sort of scavenging, which may occur after the germs have been injured or in some way affected by elements existing in the humors.

Denys[1] and Leclef were the first (1895) to produce reliable experimental evidence to prove that there exists in the blood serum of vaccinated rabbits substances which alter microbes in such a way as to permit their digestion by the leukocytes. From careful experiments *in vitro* they concluded that in a vaccinated rabbit the leukocytes obtain their power of engulfing the streptococcus from some property of the serum. The vaccinated animal fights the streptococcus, first by the direct action of its serum; secondly, by its leukocytes. The latter always owe to the serum the commencement of their power. Bordot[2] was unable to confirm these results.

Mennes[3] showed (1897) that the immunity of guinea-pigs vaccinated with toxins or cultures of pneumococci depends upon a modification of their serum whereby an active phagocytosis is produced, and that the leukocytes themselves possess no specific peculiarity. Leishman[4] devised (1902) a method of estimating quantitatively the phagocytic power of different sera to staphylococci as a measure of the resistance of such sera to infection.

Wright[5] (1902) showed that the inoculation of sterilized cultures of staphylococci in small doses raised the agglutinating power of the blood to staphylococci. A year later[6] he estimated the phagocytic index of the blood by Leishman's method, and showed that the patient's phagocytic index is raised to all staphylococci, but more decidedly to his own than to the staphylococci from some other patient.

The first mention of the word "opsonin" occurs in a communication by Wright and Douglas entitled, "The Role of Blood Fluids

[1] La Cellule, 1895, xi. p. 178.
[2] Ann. Pasteur, 1897, p. 201, note.
[3] Zeit. f. Hyg., 1897, xxv. p. 413.
[4] Brit. Med. Journ., 1902, i. p. 73.
[5] Lancet, March 29, 1902.
[6] Proc. Roy. Soc., 1903, lxxii.

in Connection with Phagocytosis."[1] They selected this word (from the Latin verb *opsono*, I prepare the food for) to characterize the substance which they believe prepares the microbes for ingestion by the phagocytes. They showed that the plasma and the serum exerted the same action upon phagocytosis, in other words, the plasma and the serum contain the same amount of opsonin. They showed that the opsonin is thermolabile, being destroyed by heating to 60°C.; that no inhibiting substances can be developed in serum by heating, because 0.85 per cent. salt solution produced no more phagocytosis than the heated serum; and that the activity of phagocytosis decreases at the same rate when unheated serum is diluted with sodium chloride as when diluted with heated serum. They proved that the serum acts upon the microbes and not upon the white corpuscles, and that the cardinal factor in phagocytosis exists in the serum.

Neufeld and Rimpau[2] (1904), without referring to Wright's work, alluded to the two well-proved antitropic elements in immune sera (that is, antitoxins and bactericidal substances), and stated that they had found a third property of immune serum, which they claimed sensitized the bacteria but did not act upon the leukocytes. They digested leukocytes in antistreptococcic serum, suspended them in normal serum, and found that they did not ingest virulent streptococci. (Note that they employed virulent organisms.) On the other hand, after treating virulent streptococci with antistreptococcic serum and then washing them free from the serum with salt solution, they found that leukocytes could then actively ingest these sensitized microbes. They obtained corresponding results with pneumococci. They proposed to call their sensitizing substances "bacteriotropic" substances. Since other distinct substances have been included under this term it seems more fitting to agree upon the very appropriate name "immune opsonins," suggested by Wright and Douglas.

Individuality of Opsonins. Sautchenko[3] and Dean[4] consider that immune serum derives its so-called opsonic action from the presence of amboceptors, because immune opsonins are relatively thermostable. Hektoen,[5] on the contrary, regards opsonins as distinct from amboceptors, and in proof of his opinion, states that normal serum under certain circumstances may possess lytic but not opsonic power, and vice versa, that immunization may give rise to opsonic but not to lytic substances, and that heat may destroy the opsonic power without affecting the lytic amboceptors, and vice versa.

[1] Proc. Roy. Soc., September 1, 1903, lxxii. p. 357; lxxiii. p. 130.
[2] Deut. med. Woch., September 29, 1904, xxx. p. 1458; Zeit. f. Hyg. u. Infect., 1905, li. p. 283.
[3] Ann. de l'Inst. Pasteur, 1902, xvi. p. 107.
[4] Proc. Roy. Soc., 1905, lxxvi. p. 506.
[5] Journ. Amer. Med. Assoc., May 12, 1906, p. 1411.

The opsonin for anthrax bacilli, present in the serum of normal dogs, is destroyed by heating at 60° C. for thirty minutes. The amboceptor for anthrax bacilli, present in the serum of normal dogs, is not affected by heating at 65° C. for thirty minutes. The serum of white rats is normally anthracidal, due to the presence of a thermostable substance that is neutralized by neutralization of the serum with oxalic acid. The same serum contains a thermostable opsonin for anthrax bacilli which, however, is not neutralized by oxalic acid.

Relation of Opsonins to Antitoxins and Bacteriolysins. We have just mentioned Neufeld and Rimpau's investigations upon antistaphylococcic and antipneumococcic sera in proof of the difference between opsonins and antitoxins and bacteriolysins. Walker's[1] experiments with diphtheria bacilli and tubercle bacilli showed that toxins as well as opsonins produce an effect upon phagocytosis, but that they act independently of one another. Opsonins may be considered analogous to toxins and complements, because they also have two distinct groups—haptophore and opsoniphore. Like complements opsonins may be neutralized or bound by various salt solutions: Ca, Ba, $MgCl_2$, K_2SO_4, $NaHCO_3$, etc., and thus prevented from acting upon bacteria.

Relation of Opsonins to Stimulins. In his treatise on Immunity, Metchnikoff described a series of experiments conducted by himself, Gengou, Klemperer, Besredka, and others, in which the introduction of serum, sometimes normal, sometimes immune, into the serum sacs of experimental animals demonstrated a greatly enhanced phagocytic activity in the leukocytes of the exudation subsequently removed from the sac for examination. To the substance which these observers conceived to be present in such sera they gave the name "stimulins," and to the presence of these stimulins in immune sera, Metchnikoff and his school attributed an important role in the processes of active and of passive immunization.

Wright and Douglas[2] endeavored to determine whether unheated serum contains "stimulins" in addition to opsonins. They found the same difference between the action of heated and of unheated serum toward staphylococci heated to 115° C. as toward living germs. Their expectations were based upon the fact that typhoid bacilli heated above 70° C. acquire a resistance to bacteriolytic effect. Although their experiments with particles of India ink and carmine were unsatisfactory, unheated serum seemed to facilitate phagocytosis of these dyes slightly more effectually than heated serum. Staphylococci + unheated serum were digested in an incubator for varying times and then divided into two portions. The first was immediately mixed with corpuscles; the second

[1] Journ. Med. Research, November, 1905, p. 178. [2] Proc. Roy. Soc., lxxii. p. 357.

was first heated to 60° C. and then mixed. In every case the phagocytic power was greater when the heating was omitted, and no difference could be detected in specimens left in the incubator fifteen minutes from those left one hour; thus they were obliged to leave the question unsolved.

Leishman[1] in 1905 showed that sera derived from cases of Malta fever or enteric fever, or from animals immunized with living cultures of the germs of these diseases, contain substances which, when added to normal human blood, are capable of increasing the phagocytic activity of the leukocytes of that blood. He also showed that these substances are specific and thermostable, withstanding a temperature of 60° C. for fifteen minutes. No evidence of the presence of these substances could be found in the sera of normal men or animals. He also showed that these substances are not identical with agglutinins, and that they act directly upon the leukocytes and not upon the bacilli. Metchnikoff suggested the name "opsonic sensitizers" for these substances. Wright suggested that they might be thermostable opsonins, in spite of the fact that opsonins act only upon the bacteria, while these substances, if the work and statement of Leishman are to be accepted as correct, act upon the leukocytes.

Specificity of Opsonins. The matter of specificity of bacterial opsonins has not yet been clearly determined, but in the case of a great many infective agents it seems to have been reasonably well established. Wright's[2] experiments showed that there was a decrease in the staphylococcic-opsonic index of serum to which typhoid bacilli had been added—which would suggest that different bacterial opsonins possess part of their power in common. Some few of our[3] sera show a variation in the opsonic index to the different organisms which we employed, notably those from a case of abscess of the liver and a case of pneumonia.

Pearce and Winne[4] showed that hæmagglutinins exist in cultures of typhoid bacilli, and Hektoen[5] believes that hæmopsonins may also be developed by bacteria. The specificity of hæmopsonins may also depend upon the types of leukocytes used; as a rule, strict specificity is usually more marked with the use of guinea-pig leukocytes than of dog leukocytes. However, immune sera, as a general rule, appear to have the most marked and earliest hæmopsonic effect upon the corpuscles used for immunization.

[1] Trans. Path. Soc., 1905, lvi. p. 344.

[2] Proc. Roy. Soc., lxxii. p. 357.

[3] These observations have been made in the Pathological Laboratory at the College of Physicians and Surgeons (Columbia University). We wish here to express our thanks to Professors Prudden and Hiss for their kindness in allowing us this privilege.

[4] Amer. Journ. Med. Sci., 1904, vol. cxviii. p. 668.

[5] Journ. Amer. Med. Assoc., May 12, 1906.

DURATION OF OPSONIC POWER. The opsonic power of serum kept at 2° C. is practically unchanged in ten days, but is destroyed in three days if the serum is kept at 37° C.[1]

DECREASE OF OPSONIC POWER. Without referring to the temperature Wright and Douglas say: "Opsonic power of blood disappears gradually on standing. In five or six days it is only about one-half as much as the original." Exposure to bright sunlight for three hours reduces opsonic value about one-third.[2]

Heat. Opsonic power is but little impaired by heat except 50° C. and above.[3] Normal human serum contains an opsonin for typhoid bacilli that resists heating above 60° C., and there is an opsonin for anthrax bacilli in serum of white rats that resists heating to 70 °C.

Dean[4] believes that some of the opsonin is unaltered even by heating to 60° C., because upon exposing bacteria to heated serum over a much longer period (Wright and Douglas originally employed fifteen minutes) some phagocytosis occurred.

Immune opsonins are more resistant to heat than the normal. Leishman[5] and his co-workers showed that the serum of persons vaccinated against typhoid fever contains sufficient opsonin to promote some degree of phagocytosis after heating to 56° C. Hektoen[6] mentions that he has several times noted a typho-opsonin in the serum of convalescents from typhoid fever which resists heating to 70° C. for thirty minutes. Immune hæmopsonins are also thermostable.

Dilution. The opsonic index of serum varies inversely as the dilution. Simon[7] has utilized this principle for determining the opsonic index.

Chemica s. Hek oen and Ruediger[8] showed that the opsonic action of serum may be diminished or inhibited by solutions (isotonic with serum) of $CaCl_2$, $BaCl_2$, $SrCl_2$, $MgCl_2$, K_2SO_4, $NaHCO_3$, $Na_3H_5C_6O_7$, $Na_2C_2O_4$, $KFe(CN)_6$, formalin, lactic acid, and chloroform. They suggest that certain so-called negatively chemotactic substances, of which lactic acid is a good example, owe their effect to neutralization or destruction of the opsonin. The diminution of resistance to various infections produced by lactic acid, and ascribed to its direct repulsion of phagocytes, is, therefore, perhaps dependent primarily upon the antiopsonic action of the acid.

[1] Jessie Horton. Duration of the Phagocytic Power of Human Leukocytes and of Opsonic Power of Human Serum Outside the Body. Trans. of the Chicago Path. Soc., April, 1905, vi.
[2] Bullock and Atkin, Proc. Roy. Soc., lxxiv. 1905.
[3] Wright and Douglas, loc. cit.
[4] Proc. Roy. Soc., G. B., 1905, vol. lxxvi. p. 506.
[5] Journ. of Hygiene, 1905, vol. v. p. 380.
[6] Loc. cit., page 1411.
[7] Johns Hopkins Hosp. Reports, January, 1906.]
[8] Journ. of Infec. Dis., 1905, vol. ii. p. 128.

Daboia Venom. The opsonic index is diminished upon digestion of serum with daboia venom.[1]

Typhoid. We have already noted that the opsonic index is diminished upon digestion with typhoid bacilli,[2] and that if other bacteria exist in serum in sufficient numbers and for a sufficient time the opsonin may be completely absorbed.

NON-BACTERIAL OPSONINS. Opsonins for cells other than bacteria have been described. Hektoen[3] found opsonins for blastomycetes and probably trypanosomes. Barrat[4] and Hektoen have observed the presence of hæmopsonins in the sera of normal animals. We, working with human sera, have observed it twice in the serum of colored people with tuberculous lesions.

RELATION OF OPSONINS TO LEUKOCYTOSIS. Huggard and Morland,[5] in their research on the therapeutic effect of the administration of yeast in tuberculosis, found that after a preliminary rise, the number of leukocytes remained constantly below normal. As the opsonic index in these cases was at first low and later high, it was apparent that there was no direct relationship here between leukocytosis and opsonic index. The opposite effect was found by Bullock and Ledingham.[6] They employed talliamine and sodium cinnamylicum, both of which increased the number of leukocytes without increasing the opsonic index—thereby sustaining this view.

SOURCE OF OPSONINS. The lack of any relation between opsonins and leukocytosis might be regarded as some evidence against Metchnikoff's belief that the leukocytes themselves furnish opsonin to the serum.

Denys and Leclef, Wright and Douglas, and Neufeld and Rimpau[7] all showed that the opsonin exists in blood serum—not in leukocytes; but none of them attempts to explain its source.

EFFECT OF DRUGS UPON OPSONINS. *Potassium Iodide.* The administration of potassium iodide has no influence upon the opsonic index. The iodide eruption is not associated with a low opsonic index. The addition of small amounts of potassium iodide to serum does not interfere with its opsonic power.[8]

Owing to the fact that nuclein has a bactericidal action and may cause leukocytosis when introduced into the blood stream, the idea occurred to Huggard and Morland,[9] in 1905, to determine whether these manifestations were also accompanied by any

[1] Wright and Douglas, Proc. Roy. Soc. lxxii. p. 357.
[2] Bullock and Atkins, ibid., lxxiv. p. 379.
[3] Loc. cit.
[4] Proc. Roy. Soc., 1905, lxxvi. p. 524.
[5] Lancet, 1905, p. 1493.
[6] Ibid., vol. ii. p. 1603.
[7] Loc. cit.
[8] British Journal of Dermatology, August, 1905.
[9] Loc cit.

change in the opsonic index after the employment of nuclein or yeast.

After a single dose of 3 grams of yeast the opsonic index dropped for two days and then rose somewhat above the normal. As has been noted, this rise in opsonic index occurred at the time when the leukocytosis was diminishing and below normal.

Huggard and Morland have made the observation that some of the lowest opsonic indices in cases of tuberculosis under their observation occurred in heavy smokers.

Relation of Virulence of Bacilli to the Tuberculo-opsonin. Denys and Leclef, Hektoen and Ruediger, and Hektoen and Horton[1] have confirmed Metchnikoff's fundamental conception that the increase of virulence of a certain organism goes hand-in-hand with its resistance to phagocytosis. They worked with streptococci, staphylococci, pneumococci, and anthrax bacilli.

Hektoen[2] concludes that the organism defends itself in one or both of two ways, that is, by producing substances which are harmful to the phagocytes, and by an increased resistance to opsonification. No observations as yet have been recorded as to the variability of the tuberculo-opsonin with tubercle bacilli of different virulence.[3]

The tuberculo-opsonic index in healthy individuals has been estimated by Bullock[4] in a series of thirty-four medical students and thirty-two nurses. The average of the sixty-six subjects was 0.95, with a maximum of 1.20 and a minimum of 0.80. Urwick[5] in twenty individuals obtained an average of 1.006.

We have made eighty-one observations[6] upon nineteen supposedly normal persons and obtained an average opsonic index of 0.988, with a maximum of 1.25 and a minimum of 0.73. We have not attempted to make a pool of a number of supposedly normal cases, as has been suggested by Wright,[7] because we have found that the normals vary to some extent, and so we have estimated three or four different normal sera separately in indexing each series of our cases. Then unless there was a considerable variation in the different normals we have struck an average with which to compare the sera to be studied. Urwick also proved that the tuberculo-opsonic index in healthy people does not vary from day to day.

Our series of nineteen normal persons estimated during the

[1] Loc. cit., p. 1413.

[2] Loc. cit., p. 1414 and 1415.

[3] Our figures have been estimated from cultures of varying virulence obtained through the kindness of Drs. Ewing, Theobald Smith, and Baldwin. We have as yet made no comparative estimates.

[4] Trans. Path. Soc., 1905, vol. lvi. p. 334.

[5] Brit. Med. Journ., July 22, 1905.

[6] For the material we wish to express our thanks to the Staffs at the New York, Roosevelt, City, French, Ruptured and Crippled, and Hudson Street Hospitals, and to Dr. Linsly R. Williams, of the Vanderbilt Clinic.

[7] Proc. Roy. Soc., G. B., 1906, vol. lxxvii. p. 194.

past three months shows the following variations in four persons: 0.84 to 1.18, 0.81 to 1.10, 0.88 to 1.10, and 0.92 to 1.06.

The tuberculo-opsonic index in different varieties of tuberculosis has been studied by a number of observers. Bullock examined 150 cases of lupus from the mildest type to the most chronic and intractable and obtained an average index of 0.75, with a minimum of 0.2 to 0.3 (three cases) and a maximum of 1.0 to 1.4 (fourteen cases). Urwick examined fifty-four cases of tuberculosis, including a number of cases of tuberculosis of the lungs in various stages.

In many of them, especially of tuberculosis of the lungs, the index was above normal, with variations from 0.3 to 2.6. In thirty-three cases of pulmonary tuberculosis, twenty-five showed an index above 1, seven below 1, and one was at 1. Wright and Douglas[1] examined sixteen cases of tuberculosis, including tuberculosis of the skin and subcutaneous tissues, tuberculous laryngitis, cystitis, peritonitis, prostatitis, and tuberculous glands. The indices ranged from 0.4 to 0.9.

We have made observations on thirty-nine cases of tuberculosis as follows: Tuberculosis of the bones, including spine, hip, knee, ankle, tarsus, and tibia—in all twenty-two—above 1 in five cases, below 1 in fourteen cases, and normal in three. In fourteen cases of pulmonary phthisis the figures vary from 0.41 to 1.37: above 1 in one case, below in eleven, and normal in two; and isolated cases of lupus and tuberculous glands, ranging from 0.96 to 1.51.

We have also estimated the tuberculo-opsonic index in a series of forty patients with varied diseases. The index was between 0.70 and 1.15 in thirty-five of these; of the remaining five there were below 0.70 four cases (two typhoids, osteomyelitis of tibia, carcinoma of stomach); above 1.15 one case, paralysis agitans with cystitis (1.38).

We have compared the tuberculo-opsonic index with the staphylococcic-opsonic, streptococcic-opsonic, pneumococcic-opsonic, gonococcic-opsonic, or colon-opsonic indices in sixteen normal subjects, in fourteen cases of tuberculosis, and in twenty-three cases of varied diseases. No marked variations occurred in the normal cases. In the tuberculous cases variations between the tuberculo-opsonic index and the staphylococcic-opsonic index ran from 2 per cent. to 50 per cent. Of the remaining twenty-three variations occurred in some cases, notably, an obscure hepatic case (cholelithiasis?): Tb. 0.96, staph. 0.85, colon 0.46; abscess of the liver: tb. 1.06, staph. 0.93, pneum. 0.72, colon 1.50; abscess of the liver: tb. 1.10, staph. 0.61, colon 0.17; chronic gonorrhœal arthritis: tb. 0.67, gon. 1.10; cirrhosis of the liver: tb. 1.13, staph. 0.45.

Methods of Determining the Tuberculo-opsonic Index. Leishman was the pioneer to devise an ingenious quantitative method

[1] Proc. Roy. Soc., 1904, vol. lxxiv.

of estimating phagocytosis. Wright's[1] modification of this method is as follows: equal volumes of (1) a bacillary emulsion in salt solution, (2) the serum to be tested, and (3) washed blood corpuscles, are measured in a capillary pipette fitted with a rubber teat, mixed thoroughly by blowing out on a slide several times, drawn up in the same pipette, the end sealed in the flame, and then incubated for fifteen or twenty minutes at 37° C. A drop of this mixture is blown out on a slide, and a smear made, fixed, and stained. The enumeration of the bacilli in twenty to fifty polymorphonuclear neutrophiles is made under a one-twelfth inch oil immersion lens, and an average per leukocyte obtained. This average divided by that for a normal serum constitutes the opsonic index.

The procedure[2] for making the suspension of tubercle bacilli is as follows: The conglomerated mass of bacilli is heated at 100° C. for ten minutes and a loopful is ground up in an agate mortar; from time to time a drop of salt solution is added until about 2 c.c. are added; it is then centrifugated in a small tube at high speed for from five to eight minutes, until the supernatant fluid is only slightly opalescent—the bacterial suspension employed.

The washed corpuscles are obtained by receiving 20 to 40 drops of blood into about 30 c.c. of 1 per cent. sodium citrate in 0.85 per cent. sodium chloride solution. After centrifugating, the supernatant fluid is pipetted off and 0.85 per cent. NaCl is substituted. They are washed thus twice and finally the salt solution is pipetted off and the upper layer of the corpuscles which is rich in leukocytes is taken for the washed corpuscles. This should be quite thick in order to make good smears and to prevent the leukocytes from breaking up.

The serum is obtained by receiving the blood to be tested in small glass capsules with curved capillary limb, allowing it to clot, and then centrifugating so that the clear serum is easily accessible.

Our slides for tubercle bacilli have been fixed in formalin vapor, stained in aniline fuchsin, decolorized in acid alcohol, washed in 1 to 1000 sodium carbonate solution, and counterstained with methylene blue.

Difficulties. Of course, in a method of this kind there are many difficulties and sources of error, and an enumeration of some of those which we have met may prove helpful to others. The most difficult thing of all is to get a bacillary emulsion free from clumps and of the right strength. If too thick, the bacilli cannot be counted accurately; and if too thin, there will not be enough to strike a proper average. Counts averaging from two to five

[1] Proc. Roy. Soc., 1903, vol. lxxii. and 1904, lxxiii.

[2] We have followed the details of this technique—essentially those of Wright—to whom we wish to express our hearty thanks for his kindness in personally explaining his methods to one of us.

bacilli per leukocyte are to be desired. The varying opalescence of a series of tubes of barium sulphate suspension of different strengths will serve as a comparison of the thickness of the bacterial emulsion.[1] With tubercle bacilli an added difficulty is that after the bacilli are separated they are clumped by salt solutions of any concentration greater than 0.1 per cent., and unheated bacilli are agglutinated by any blood serum. To prevent this clumping, the bacilli are heated at 100° C. for ten to fifteen minutes, and the suspension is made in 0.1 per cent. salt solution.

For the sake of accuracy the capillary pipettes should be of approximately the same calibre. The "leukocytic cream" should be used fresh, otherwise the leukocytes tend to stick together.

Smears are best made by using a slide with the corner broken off and the end made rough with a file. The smears should be fairly thick and are made best by pushing the smearer. The edges of the smears are counted because most of the leukocytes collect there. It is better to select isolated leukocytes for counting or at most bunches of only two or three, as the counts for these are more uniform than when large masses of leukocytes are counted. Cleanliness, speed, and accuracy are essential to good technique.

Diagnostic Value of the Tuberculo-opsonic Index. The diagnostic value of the tuberculo-opsonic index is a subject which is just beginning to be worked upon.

Wright and Reid[2] have furnished the only contribution. Their conclusions are:

1. Where a series of measurements of the opsonic index of the blood is persistently low, it may be inferred in the case where there is evidence of a localized bacterial infection which suggests tuberculosis that the infection is tuberculous in character.

2. Where repeated examination reveals a persistently normal tuberculo-opsonic index, the diagnosis of tuberculosis may with probability be excluded.

3. Where there is revealed by a series of blood examinations a constantly fluctuating opsonic index, the presence of active tuberculosis may be inferred.

4. When there is only a single blood examination—if this is low, tuberculosis, either localized or systemic, may be inferred. If the tuberculo-opsonic index is high, systemic tuberculous infection which is active or has recently been active may be inferred. If the tuberculo-opsonic index is normal or nearly normal, neither a negative nor positive conclusion is warranted. Our observations tend to confirm this statement.

5. Since there are developed in blood serum in those undergoing

[1] Suggested by McFarland. Medicine, April, 1906

[2] Proc. Roy. Soc., 1906, vol. lxxvii.

inoculation with tubercle vaccine, or, as the case may be, in those who have responded to tuberculous infection, certain opsonic-like substances which resist heating to 60° C. for ten minutes, tuberculosis in those whose serum retains in any considerable degree the power of inciting phagocytosis after it has been so heated may be inferred.

Whether this point can be of much diagnostic value would seem rather doubtful from our observations. In a series of sixteen sera derived from different varieties of tuberculosis, we found the tuberculo-opsonic index of the unheated sera varied from 0.41 to 1.20; that of sera heated at 60° C. for ten minutes varied between 0.00 and 0.20. In five normal control sera the index of the unheated sera varied from 1.0 to 1.08; that of the heated sera from 0.02 to 0.60.

In another series we found that heating at 50° C. for ten minutes only slightly diminished the index of the heated as compared with the unheated serum. There was no difference between the normal and the tuberculous individuals. In both the above series we employed an emulsion of bacilli in 1.6 per cent. salt solution.

In a further small series we heated at 60° C. for ten minutes, employing an emulsion of bacilli in 0.1 per cent. salt solution. The figures obtained were as follows:

	Unheated.	Heated.
Tuberculous ankle, ante-operation	0.89	0.45
Tuberculous ankle, post-operation	1.26	1.60
Normal	1.00	0.23
Normal	1.17	0.24
Pneumonia, tuberculous	0.84	0.30
Pneumonia, tuberculous	0.86	0.20
Normal	1.02	0.14
Normal	0.73	0.14

Attention has been called to the supposition that the bacilli grow in regions of low bacterio-tropic pressure, and observations tend to show that fluids or pus from such regions contain a much smaller amount of opsonin than the blood serum obtained in the usual way from the finger. Hence, when the tuberculo-opsonic index of such fluids is much lower than that of the blood serum the presence of a tuberculous infection may be inferred.

Thus far we have estimated the opsonic index in four such cases, as follows:

CASE I.—Herpes zoster with hydrothorax: tuberculo-opsonic index of blood serum, 1; tuberculo-opsonic index of chest fluid, 1.

CASE II.—Tuberculous caries of the spine with empyema: tuberculo-opsonic index of blood serum, 0.8; tuberculo-opsonic index of pus from chest, 0.3.

CASE III.—Tuberculous pleurisy with effusion: tuberculo-opsonic index of blood serum, 0.78; tuberculo-opsonic index of chest fluid,

0.89. In this case the pneumococcic opsonic index of blood serum was 1.09; chest fluid, 0.95.

CASE IV.—Empyema following pneumonia: tuberculo-opsonic index of blood serum, 0.84; tuberculo-opsonic index of pus from chest, 0.00°.

THE EFFECT OF TUBERCULIN ON TUBERCULO-OPSONIC INDEX. "A vaccine" is defined by Wright[1] to be "any chemical substance which when introduced into the organism causes there an elaboration of protective substances, or a vaccine is a substance which induces in the organism an elaboration of bacterio-tropic elements. A tubercle vaccine is one which induces an elaboration of tuberculo-tropins."

CHART 1

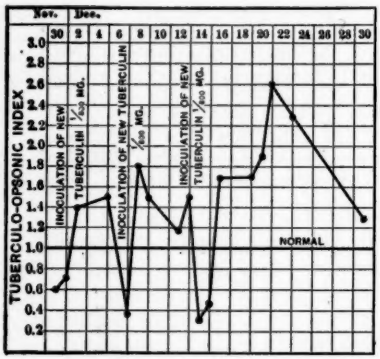
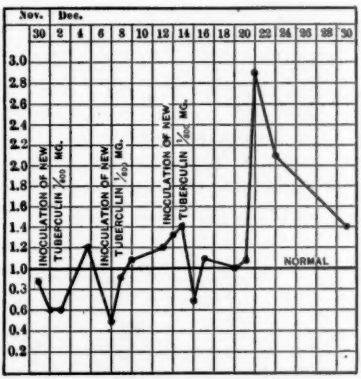

Nov.
Dec.
30 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
TUBERCULO-OPSONIC INDEX
3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2
INOCULATION OF NEW TUBERCULIN 1/60 MG.
INOCULATION OF NEW TUBERCULIN 1/60 MG.
INOCULATION OF NEW TUBERCULIN 1/60 MG.
NORMAL

CHART 2


Nov.
Dec.
30 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.3 0.6 0.4 0.2
INOCULATION OF NEW TUBERCULIN 1/60 MG.
INOCULATION OF NEW TUBERCULIN 1/60 MG.
INOCULATION OF NEW TUBERCULIN 1/60 MG.
NORMAL

Relating to H. and D., two children with tuberculous glands, who were treated with therapeutic inoculations of T. R. The curves show the condition of the blood before inoculation and the changes in the tuberculo-opsonic power which supervened upon the first three inoculations.—Wright, Medico-Chirurg. Transactions, 1905, vol. lxxxix. p. 5.

Tuberculin, or a tubercle vaccine, is always a derivative of the bacterial cell and when inoculated withdraws from the organism a certain amount of protective substances. Deprived of the tuberculo-tropic substance, the cells are stimulated and replace not only that which is withdrawn, but more.

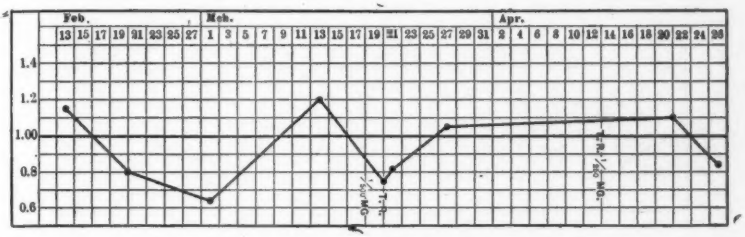
Immediately after the injection of tuberculin there is a period of diminished resistance, shown by diminution of protective elements in the blood, both agglutinins[2] and opsonins—it would seem the so-called "negative phase;" succeeding this, there is an inflowing of, and consequent increase in, the protective elements—"positive phase." Most of these protective elements rapidly disappear, but leave behind in the blood a more or less permanent

[1] The Clinical Journal, November 9, 1904.
[2] Wright, Lancet, May 9, 1903.

increase over the original. Wright speaks of the whole sequence as the "Law of the ebb and flow, and reflow and maintained high tide of immunity." This is illustrated in the accompanying Charts 1 and 2.

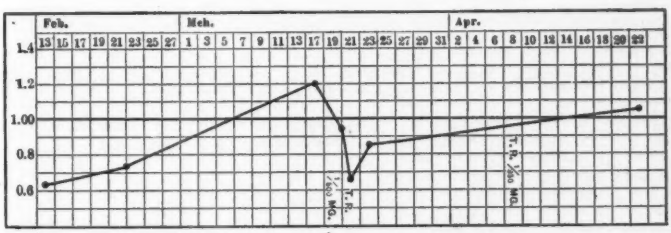
This train of events succeeds inoculation of vaccine sufficient to cause a constitutional disturbance. When only a small dose of vaccine is given, the negative phase may be so insignificant and of such short duration as not to be capable of measurement, and the positive phase will be correspondingly diminished. On the

CHART 3



Patient S. Tuberculosis of the hip, with marked improvement clinically.

CHART 4



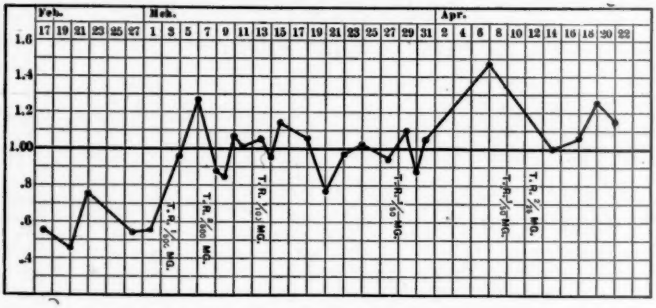
M. S., aged fifty years. Lupus of long standing; slight improvement only.

other hand, if the dose of vaccine is too large, the negative phase will be unduly prolonged and a positive phase may not appear at all. The question of dose, then, is of the greatest importance, for if too little is employed no therapeutic effect will result; while on the other hand, too large a dose is dangerous and so lowers the resistance of the organism as to favor the multiplication of the bacteria. Such dangers with a single inoculation are, of course, greatly magnified by repeated inoculations. If a series of such inoculations is attempted during the negative phase, there will

result a further fall in the protective substances or a "cumulation in the direction of the negative phase."

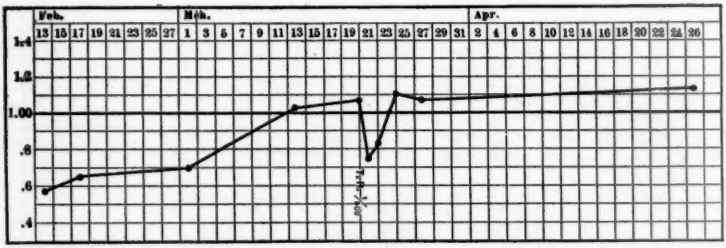
Wright and his associates consider that the result of the vaccination cannot be estimated from the character of the constitutional disturbance, but with some reason urge the daily determination of the opsonic index to measure the effect.

CHART 5



Patient K. G. Tuberculosis of the ankle; no improvement.

CHART 6



Patient S. Tuberculosis of the ankle; slight improvement.

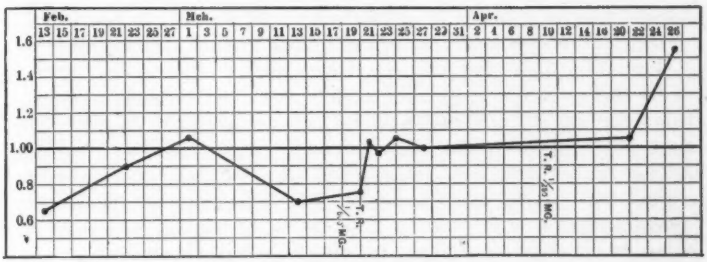
Wright[1] advises the smallest possible initial dose sufficient to produce any negative phase, and re-inoculation only after the subsequent positive phase has begun to diminish.

Sooner or later a point will be reached when the organism ceases to respond to inoculation, and further doses of vaccine not only do no good, but may bring the content of the blood in protective substances to a lower level than that from which it originally started.

[1] Lancet, December 2, 1905, p. 1598.

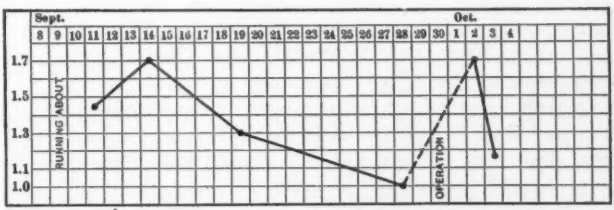
The appended curves of patients with tuberculous disease show the variations in the tuberculo-opsonic index as a result of our tuberculin inoculations.

CHART 7



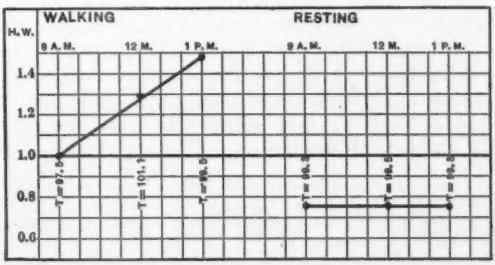
Patient M. S. Tuberculosis of the ankle; slight improvement.

CHART 8



Shows in the case of a child with tuberculous caries of the fibula that the tuberculo-opsonic power may be raised by active exercise and surgical procedures.

CHART 9



Shows in a case of pulmonary tuberculosis undergoing sanitarium treatment how exercise may influence the tuberculo-opsonic index. Dr. J. Freeman, curve used by Wright.—Medico-Chirurg. Transactions, 1905, vol. lxxxix. p. 17.

The tubercle vaccine employed was Koch's T. R., tuberculin.[1] 1 c.c. of T. R. equal to 1 milligram of tubercle powder. Wright advises that the initial dose should not exceed $\frac{1}{1000}$ milligram.

The cases treated by T. R. controlled by the estimation of the tuberculo-opsonic index reported thus far, consist entirely of localized tuberculous infections and include, tuberculous peritonitis, cystitis, glands and sinuses following an operation for their removal, tuberculosis of the subcutaneous tissues, lupus, etc.[2]

The danger underlying the treatment of any active process in the lungs is very great, for such a case is absorbing tuberculin from the site of infection and his life according to Wright consists of a succession of negative and positive phases. So long as we cannot regulate the amount of bacterial substances absorbed, the physician would only be adding to the danger by inoculating the tuberculin. This refers, of course, especially to those cases of tuberculosis running a temperature, which are more or less systemic infections.

Charts 8 and 9 show how exercise and operation may influence the opsonic index by increasing the flow of lymph through tuberculous foci, the result being as if tuberculin had been administered. They serve also to show how dangerous it might be further to inoculate such cases, there being no way, of course, to regulate the dose of tuberculin absorbed by the organism from *his own* focus or foci of infection.

Wright also cites two phthisical patients whose indices had never been lower than 1. They took part in a dance, both became ill; and their indices declined to 0.12 and 0.33 respectively; another phthisical patient whose index fell as a result of overwork to 0.2 from a level of over 1.

We have not attempted to criticise any of the work outlined above, for the evident reason that our subject is merely a review. The delay in mastering the difficulties of the technique, despite the good fortune of one of us in seeing Prof. Wright and his associates at work, and the comparatively few observations we have made, would in any event prohibit a very definite opinion upon our part. Although diagnosis may not be materially aided, and treatment particularly with tuberculin, as suggested by Dr. Kinghorn, may not require such elaborate and repeated blood examinations, it may be that some assistance toward accuracy of prognosis may be forthcoming. Continued observations will decide.

[1] The effect of protective inoculation of tubercle vaccine on rabbits has been studied by E. R. Baldwin (Medical News, September 30, 1905) and his associates at Saranac Lake, New York, with somewhat negative results as to the opsonic content of bloods compared with the agglutinating reaction, and would seem to be rather more complex than Wright believes.

[2] Wright, loc. cit.

THE TECHNIQUE OF THE TUBERCULO-OPSONIC TEST.[1]

By Hugh M. Kinghorn, M.D.,
and
David C. Twichell, M.D.,
of Saranac Lake, New York.

(From the Saranac Laboratory, Dr. E. L. Trudeau, Director.)

According to Professor A. E. Wright, the phagocytic effect obtained when bacteria are introduced into the blood is dependent upon an action exerted by the blood fluids directly upon the micro-organisms. He speaks of this action, which prepares the micro-organisms for phagocytosis, as an opsonic action (Latin: *opsono*, I cook, I prepare pabulum for). It is due to the presence in the blood fluids of substances he calls opsonins. Opsonins for tuberculosis are substances which modify tubercle bacilli in a manner which renders them an easy prey for the phagocytes.

The following observations have been made by Professor Wright and Captain S. R. Douglas: (1) Opsonins are contained in the blood fluids—serum or plasma; (2) they lose their power when heated to 60 to 65° C. for ten to fifteen minutes; and (3) they exercise their influence by effecting a modification in the bacilli, and not by exerting a direct stimulating effect upon the phagocytes.

The object of this paper is to discuss the technique of the method used in estimating the opsonic power in the blood of tuberculous patients, and also of those undergoing tuberculin treatment, and to record our experience with it. Briefly, the method employed by Professor Wright is as follows:

Equal quantities of the patient's serum, an emulsion of tubercle bacilli, and white blood corpuscles (washed in 0.5 per cent. sodium citrate in normal salt solution) are mixed in a capillary pipette and incubated at 37° C. for twenty minutes, after which blood films are made of the mixture and stained for tubercle bacilli. The average number of tubercle bacilli ingested by each polymorphonuclear white corpuscle is calculated, and the figure thus obtained is called the phagocytic index. The opsonic index is the result obtained by dividing the number of bacteria taken up per leukocyte in the presence of any given serum by the number taken up per leukocyte in the presence of the serum of a normal individual, which latter is regarded as unity. For example, the number of tubercle bacilli per leukocyte in the presence of a given serum = 3.

[1] Read at the meeting of the National Association for the Study and Prevention of Tuberculosis, Washington, D. C., May 17 and 18, 1906.

Tubercle bacilli per leukocyte in the presence of a healthy serum=2

2:3::1: opsonic index = 1.5.

The difficulties which we experienced in the Saranac Laboratory in using this tuberculo-opsonic test of Wright were considerable. We, therefore, purpose to give the various steps in detail, together with modifications which we have tried.

Method of Obtaining Washed Leukocytes. It was found by Wright and Douglas that the source of the white corpuscles used made no difference in the result; in fact they can be taken from the patient or from some healthy person. An inferior position is, therefore, assigned to the source of the polynuclear white cells in the work of phagocytosis as compared with the serum.

To obtain the blood we make a prick in the side of a finger with a needle, and wind a piece of string around the finger from above downward in order to render it turgid. As the blood emerges from the prick, we draw it into a pipette containing a small amount of 0.5 per cent. sodium citrate solution in 0.85 per cent. NaCl. A 10 c.c. pipette, with a bulb and a short stem drawn to a fine point, allows thorough mixing of the blood and citrate solution. The citrate solution prevents the blood from clotting. After each large drop of blood is drawn into the pipette, we draw up a little more citrate solution and shake gently. From six to ten large drops of blood are sufficient. This mixture of blood and citrate solution is then centrifugalized in narrow tubes, the supernatant solution drawn off, and then about the same quantity of 0.85 per cent. NaCl solution thoroughly mixed with the blood. This mixture is then centrifugalized, the supernatant solution drawn off, care being taken not to draw too close to the corpuscle sediment lest the layer of white cells be disturbed. This layer of white cells, called "blood cream" by Wright, is then carefully drawn off from the blood and thoroughly mixed. Formerly Professor Wright used four washings, the first with the citrate, and the remaining three with 0.85 NaCl. At present two washings are used, and we find it sufficient.

Method of Obtaining the Emulsion of Tubercle Bacilli for Phagocytosis. Considerable difficulty has been experienced by almost all who have used the tuberculo-opsonic test in obtaining a suitable emulsion of bacilli. This is due to the fact that the bacilli appear so frequently in clumps and not separated homogeneously.

At the very outset a twofold technical difficulty confronted Wright and Douglas in preparing their emulsions. The first difficulty was associated with the fact that the tubercle bacillus occurs in ordinary cultures in agglomerated masses. The second difficulty is due to the fact that unaltered tubercle bacilli, when they have been obtained in homogeneous suspension, are agglu-

tinated by the action of both serum and physiological salt solution. They overcame the first difficulty by breaking up the bacterial masses in a mortar in a 0.1 per cent. salt solution, that is, in a salt solution diluted up to the point at which it will no longer bring together by its agglutinating action tubercle bacilli which have been mechanically separated. The second difficulty was overcome by heating the tubercle culture to 100° C.

In a private communication recently received from Dr. George W. Ross, an assistant of Professor Wright, the following directions were given to obtain an emulsion of tubercle bacilli such as they now use:

1. "If you use the glycerin suspension of tubercle bacilli (such as is left after making old tuberculin) you must first wash out the glycerin by means of water and filter paper—ending up the final washing with 1.5 per cent. solution of NaCl.

2. "Next transfer to a small agate mortar (one to one and one-half inch in diameter) and rub up the washed tubercle bacilli to a paste; that is, use only a little of the 1.5 per cent. salt solution to begin with. Keep rubbing up, continually adding more salt solution until you have an emulsion which has the opalescence of thick ground-glass.

3. "Centrifugate for some minutes to drive down the larger clumps.

4. "Pipette off the supernatant emulsion. As a rule this requires further diluting with the 1.5 per cent. salt solution. The extent of this is only learned by putting up trial tubes with serum and corpuscles. For example, if in the trial experiment the leukocytes contain clumps of say four or five bacteria each, you will know that further dilution and centrifugalization are necessary. Use always a 1.5 per cent. salt solution.

"From one to two tubercle bacilli per cell is a convenient average."

In our own work we have, however, used a different emulsion, prepared by Dr. E. R. Baldwin, who tried to improve the method by removing some of the wax from the bacilli, and thus to render them free from clumps. He did this by extraction with chloroform, as follows:

(*a*) A quantity of tubercle bacilli from broth cultures was washed until free from all traces of the culture medium. After drying these in the desiccator, 150 grams were pounded and rubbed to a fine powder in a mortar to break up the large clumps.

(*b*) This powder was then placed in a flask with chloroform. The flask was heated on a water-bath with a return condenser. The emulsion was then filtered on hard filter paper. The residue was washed with hot chloroform, and afterward evaporated by exposing the filter to air and then in the desiccator. This residue was again rubbed in a mortar, and extracted again in the same manner.

(*c*) The washed residue was finally suspended in 185 c.c. cold chloroform and used as a stock emulsion.

To obtain a suspension from this stock emulsion our procedure is as follows: 0.3 c.c. of the chloroform emulsion is measured off and put into a small mortar; the chloroform is allowed to evaporate, which it does almost instantly, and the dry white powder that remains is rubbed up with 1 c.c. of 0.1 per cent. NaCl. First it is rubbed in a small quantity of this salt solution, and then the remainder is slowly added. This emulsion is then transferred to a small centrifugating tube and centrifugalized for five minutes, at definite speed, to throw down the coarse clumps. A small quantity of the supernatant fluid is drawn off and thoroughly mixed. If one draws directly from the emulsion which remains in the centrifugating tube, when first the test is made, one may draw from different layers and thus render the test inaccurate. The emulsion thus obtained is of very uniform density and free from clumps. The only objection is that some of the bacilli appear feebly stained. A further objection may be made that alterations are produced in the bacilli by the extraction with chloroform. Comparative tests, however, with simply sterilized bacilli, have shown that the same relation may be expected in the phagocytic activity in each of them. Since the object of the test is to compare the opsonic strength of different serums, the particular form of the emulsion which gives the most accurate results is the only factor of importance.[1]

METHOD OF OBTAINING THE SERUMS. When an opsonic test is made we need some standard for comparison. At present the fresh mixed serums of several healthy persons are used as the standard serum by Professor Wright, and this mixed serum is regarded as unity.

The use of this standard is justified by the following facts: (1) The opsonic power is approximately the same in all healthy people, and (2) the opsonic power of healthy people varies very slightly, or not at all, from day to day.

It is found that the opsonic power decreases gradually after the serum has been withdrawn from the body, and it is, therefore, necessary that the standard serum and the serum to be tested should be withdrawn within a few hours of each other. Wright found that the opsonic power of the serum diminished but slightly up to twelve to eighteen hours, but that after that it diminished considerably. In our work thus far we have used but one normal serum for a standard.

METHOD OF MIXING AND INCUBATING THE WASHED LEUKOCYTES, THE SERUM, AND THE EMULSION OF TUBERCLE BACILLI. Having obtained the washed leukocytes, the serum, and the emulsion we then proceed to make the test.

[1] Instead of the chloroform emulsion, we now use an emulsion prepared according to Wright's method, and find it very satisfactory.

We make the pipette, into which they are drawn, in the following way: A piece of glass tubing, about one-quarter inch in diameter and from four to five inches in length, is heated over a flame and drawn out as fine as possible, and divided in the middle. The stem of this is about two inches in length, and the drawn-out part about seven to eight inches. At a point about one to one and one-half inches from the capillary end a mark is made with a blue or red pencil. This serves to measure the serum, emulsion, and corpuscles. By placing a closely fitting rubber nipple over the end of the stem, and by packing the stem for a short distance by two small layers of absorbent cotton, and between these a small layer of some powder, such as plaster-of-Paris or chalk, it is an easy matter to draw up to the index the serum emulsion and corpuscles, and to allow a small space of air between each of these. The tip of the pipette is wiped off after each operation.

The three are then expelled into a small tapering tube about one-eighth inch in diameter, one inch long and closed at one end, and thoroughly mixed by drawing the liquid in and out. The mixture is then again drawn into the pipette, the end sealed in a flame, and placed in the incubator at 37° C. for twenty minutes. On removing the pipette from the incubator the contents are again thoroughly mixed in another small tube, as described above, and slide smears are then made.

Method of Preparing Slides for the Reception of Blood Films. Professor Wright's method is as follows: He says that the really important thing in connection with the slide is to be sure that its surface shall be rough. The polishing of the surface and the defective adherence between the blood and the slide which results from it furnish the opportunity for the piling up of the corpuscles one upon another, under the influence of the surface tension of the fluid. The polishing of the slide is, in other words, directly responsible for the patchiness of the ordinary blood film. He therefore finds it of benefit to boil all slides in strong caustic potash until their surface has become definitely hazy. This haziness depends upon inequalities of the surface, and it disappears when the surface oil or Canada balsam is placed upon the slide.

A still better method, also described by Wright, is to rub the surface of the slide with emery paper. He employs the finest variety of emery paper, and in order to obtain the necessary mechanical pressure mounts the emery paper by means of a rubber ring upon a stout cylindrical ruler.

Method of Hardening and Staining the Slides. Professor Wright's present method is to fix the blood films in saturated corrosive sublimate, stain with boiling carbol-fuchsin, decolorize with 2 per cent. sulphuric acid, and counterstain with methylene blue after washing in 1 to 1000 sodium carbonate.

Our method has been to fix with wood alcohol for several minutes,

heat in the incubator at 37° C. for ten minutes in aniline-fuchsin, decolorize with 0.5 per cent. hydrochloric acid in 50 per cent. alcohol, and counterstain with Wright's stain. Wright's blood stain (James H. Wright) for counterstaining has proved superior in our hands to any other. We use it diluted with two parts of wood alcohol. The films are then dried and examined.

NUMBER OF CELLS NECESSARY TO COUNT. In the various published works by Professor Wright and his associates it would appear that the count from a comparatively small number of leukocytes was thought sufficient for the determination of the opsonic index. We have paid special attention to this point in order to satisfy ourselves as to the usefulness of the test so far as tuberculosis is concerned. While it is true that the bacilli counted in 20 to 30 leukocytes may indicate in some cases the correct relation between a normal and a tuberculous serum, when all the conditions are favorable as to sera and technique, we have found that an accurate count requires from 100 to 200 cells. Some examples showing the variations encountered are appended.

Up to the present time our work has been mainly confined to technique, and to testing the blood of patients who are taking tuberculin treatment. Our results are too few to give any definite conclusions, and we intend to give these at a later date.

The following counts of 200 polynuclear cells show the variations in groups of 25, 50, 100, and 200 cells:

EXPERIMENT 30, MARCH 27, 1906.

K.'s washed corpuscles..... 1 vol.
J. P.'s serum..... 1 vol.
Suspension of tubercle bacilli. 1 vol.
(The whole incubated at 37° C. for twenty minutes.)
(t. b. = tubercle bacilli.)

1st	25	polynuclear cells	=	27	t. b.	= average of	1.08	t. b.	per cell
2d	"	"	"	27	"	"	1.08	"	"
3d	"	"	"	39	"	"	1.56	"	"
4th	"	"	"	31	"	"	1.24	"	"
5th	"	"	"	24	"	"	0.96	"	"
6th	"	"	"	30	"	"	1.20	"	"
7th	"	"	"	24	"	"	0.66	"	"
8th	"	"	"	45	"	"	1.80	"	"
1st	50	polynuclear cells	=	54	t. b.	= average of	1.08	t. b.	per cell.
2d	"	"	"	70	"	"	1.40	"	"
3d	"	"	"	54	"	"	1.08	"	"
4th	"	"	"	69	"	"	1.38	"	"
1st	100	polynuclear cells	=	124	t. b.	= average of	1.24	t. b.	per cell
2d	"	"	"	123	"	"	1.23	"	"
1st	200	polynuclear cells	=	247	t. b.	= average of	1.23	t. b.	per cell.

Experiment 30, March 27, 1906.

K.'s washed corpuscles..... 1 vol.
D. C. T.'s serum..... 1 vol.
Suspension of tubercle bacilli 1 vol.
(The whole incubated at 37° C. for twenty minutes.)

1st	25	polynuclear cells =	22	t. b. =	average of	0.88	t. b.	per cell
2d	"	" "	27	"	"	1.08	"	"
3d	"	" "	26	"	"	1.04	"	"
4th	"	" "	27	"	"	1.08	"	"
5th	"	" "	21	"	"	0.84	"	"
6th	"	" "	38	"	"	1.52	"	"
7th	"	" "	38	"	"	1.52	"	"
8th	"	" "	33	"	"	1.32	"	"
1st	50	polynuclear cells =	49	t. b. =	average of	0.98	t. b.	per cell
2d	"	" "	53	"	"	1.06	"	"
3d	"	" "	59	"	"	1.18	"	"
4th	"	" "	71	"	"	1.42	"	"
1st	100	polynuclear cells =	102	t. b. =	average of	1.02	t. b.	per cell
2d	"	" "	130	"	"	1.30	"	"
1st	200	polynuclear cells =	232	t. b. =	average of	1.16	t. b.	per cell

Experiment 32, March 29, 1906.

K.'s white blood corpuscles... 1 vol.
J. P.'s serum..... 1 vol.
Suspension of tubercle bacilli 1 vol.
(The whole incubated at 37° C. for twenty minutes.)

1st	25	polynuclear cells =	34	t. b. =	average of	1.36	t. b.	per cell
2d	"	" "	31	"	"	1.24	"	"
3d	"	" "	34	"	"	1.36	"	"
4th	"	" "	49	"	"	1.96	"	"
5th	"	" "	39	"	"	1.56	"	"
6th	"	" "	31	"	"	1.24	"	"
7th	"	" "	41	"	"	1.64	"	"
8th	"	" "	22	"	"	0.88	"	"
1st	50	polynuclear cells =	65	t. b. =	average of	1.3	t. b	per cell
2d	"	" "	83	"	"	1.66	"	"
3d	"	" "	70	"	"	1.40	"	"
4th	"	" "	63	"	"	1.26	"	"
1st	100	polynuclear cells =	148	t. b. =	average of	1.48	"	"
2d	"	" "	133	"	"	1.33	"	"
1st	200	polynuclear cells =	281	t. b. =	average of	1 41	t. b.	per cell

Experiment 32, March 29, 1906.

K.'s white blood corpuscles..... 1 vol.
T.'s serum..... 1 vol.
Suspension of tubercle bacilli 1 vol.
(The whole incubated at 37° C. for twenty minutes.)

1st	25	polynuclear cells =	53	t. b. =	average of	2.12	t. b.	per cell
2d	"	" "	51	"	"	2.04	"	"
3d	"	" "	45	"	"	1.80	"	"
4th	"	" "	56	"	"	2 24	"	"
5th	"	" "	27	"	"	1.08	"	"
6th	"	" "	49	"	"	1.96	"	"
7th	"	" "	38	"	"	1.52	"	"
8th	"	" "	27	"	"	1.08	"	"
1st	50	polynuclear cells =	104	t. b. =	average of	2.08	t. b.	per cell
2d	"	" "	101	"	"	2 02	"	"
3d	"	" "	76	"	"	1.52	"	"
4th	"	" "	65	"	"	1.30	"	"
1st	100	polynuclear cells =	205	t. b. =	average of	2.05	t. b.	per cell
2d	"	" "	141	"	"	1.41	"	"
1st	200	polynuclear cells =	346	t. b. =	average of	1.73	t. b.	per cell

EXPERIMENT 33, MARCH 30, 1906.

T.'s white blood corpuscles... 1 vol.
J. P.'s serum..... 1 vol.
Suspension of tubercle bacilli 1 vol.
(The whole incubated at 37° C. for twenty minutes.)

1st	25	polynuclear cells =	113	t. b. =	average of	4.52	t. b.	per cell
2d	"	"	"	97	"	"	3.88	"	"
3d	"	"	"	88	"	"	3.52	"	"
4th	"	"	"	109	"	"	4.36	"	"
5th	"	"	"	98	"	"	3.92	"	"
6th	"	"	"	115	"	"	4.60	"	"
7th	"	"	"	115	"	"	4.60	"	"
8th	"	"	"	114	"	"	4.56	"	"
1st	50	polynuclear cells =	210	t. b. =	average of	4.2	t. b.	per cell
2d	"	"	"	197	"	"	3.94	"	"
3d	"	"	"	213	"	"	4.26	"	"
4th	"	"	"	229	"	"	4.58	"	"
1st	100	polynuclear cells =	407	t. b. =	average of	4.07	t. b.	per cell
2d	"	"	"	442	"	"	4.42	"	"
1st	200	polynuclear cells =	849	t. b. =	average of	4.24	t. b.	per cell

EXPERIMENT 33, MARCH 30, 1906.

T.'s white blood corpuscles... 1 vol.
K.'s serum..... 1 vol.
Suspension of tubercle bacilli 1 vol.
(The whole incubated 37° C. for twenty minutes.)

1st	25	polynuclear cells =	100	t. b. =	average of	4.00	t. b.	per cell
2d	"	"	"	103	"	"	4.12	"	"
3d	"	"	"	58	"	"	2.32	"	"
4th	"	"	"	77	"	"	3.08	"	"
5th	"	"	"	115	"	"	4.60	"	"
6th	"	"	"	81	"	"	3.24	"	"
7th	"	"	"	84	"	"	3.36	"	"
8th	"	"	"	96	"	"	3.84	"	"
1st	50	polynuclear cells =	203	t. b. =	average of	4.06	"	"
2d	"	"	"	135	"	"	2.70	"	"
3d	"	"	"	196	"	"	3.92	"	"
4th	"	"	"	180	"	"	3.60	"	"
1st	100	polynuclear cells =	338	t. b. =	average of	3.38	t. b.	per cell
2d	"	"	"	376	"	"	3.76	"	"
1st	200	polynuclear cells =	714	t. b. =	average of	3.57	t. b.	per cell

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A SUGGESTION IN THE TREATMENT OF HÆMOPTYSIS.[1]

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THE cause and treatment of pulmonary hemorrhage have interested physicians since the time "when the memory of man runneth not to the contrary." Its importance in pulmonary tuberculosis has long been known, though it is more recently that its true relation

[1] Read at the meeting of the National Association for the Study and Prevention of Tuberculosis, Washington, D. C., May 17 and 18, 1906.

to the disease has been established. Long a moot point in medicine, hæmoptysis has been held by many famous authorities, among them Hippocrates, Galen, Aretæus, Hoffman, Boerhaave, Van Swieten, Graves, and Niemeyer, as a precursor and even the cause of pulmonary tuberculosis. Opposed to them stood Richard Morton, Portal, Bayle, Laënnec, and Louis. Walshe, in the middle of the last century, showed clearly that Laënnec and Louis were correct in holding that in most instances symptoms preceded the hæmoptysis which should, therefore, be looked upon rather as the result than as the cause of the pulmonary tuberculosis. A few years later, 1868, Rasmussen, of Copenhagen, published in the *Edinburgh Medical Journal* his pathological researches upon the origin of hæmoptysis. He showed, as is well known, that fatal hæmoptysis proceeds from a ruptured aneurysm in a pulmonary vessel. Since then it has been clearly established that fatal hæmoptysis is due in practically all cases to the rupture of an aneurysm situated upon a branch of the pulmonary artery. Few, I might say almost no, well authenticated cases of fatal hæmoptysis have occurred from rupture of the pulmonary vein or of the bronchial artery. It has long been known that the walls of the pulmonary vessels are quickly attacked in tuberculosis. The endarteritis itself is usually obliterating. Even when this does not occur the vessel walls are thickened and immobile.

The pulmonary blood pressure may be affected by change in the calibre of the bloodvessels, in the greater or lesser circulation, by increased or lessened flow of blood, by change in the rate of circulation, and by failure of the left side of the heart to perform properly its function. Recent work has thrown much doubt upon the existence of vasomotor nerves in the pulmonary vessels and it is probable that, cæteris paribus, the pulmonary pressure is directly determined by the amount of blood supplied to the right ventricle.

Theoretically, hæmoptysis may be controlled by increasing the coagulability of the blood, by lessening the rapidity of its flow, by reducing the volume of blood in the weakened vessel, by lowering the blood pressure, or by constricting the affected vessel, which may act in one of the ways heretofore mentioned. Calcium chloride has not accomplished in my hands what I was led to hope for from Wright's experiments. Digitalis has often signally failed to be of any benefit. The pathological changes occurring in the pulmonary vessels in the diseased area preclude any changes in their calibre. All drugs, therefore, which cause a contraction of the bloodvessels, such as ergot or adrenalin, would, if they acted upon the pulmonary vessels, be directly injurious, as they would cause a contraction of the healthy vessels, and the diseased vessels, incapable of varying in diameter, would be subjected to increased instead of lessened tension. Recent experimental work, which has been mentioned, would seem to indicate that lessened tension

from dilatation of the other pulmonary vessels does not take place.

For these reasons we must seek elsewhere to regulate the pulmonary tension, and in considering the subject the first thought is to lower the tension by reducing the volume of blood in the circulation. All severe hæmoptyses act quickly in this way and in most instances render venesection useless and even dangerous. Another attempt in the same direction is ligation of the limbs, a modern modification of Junod's boot.

More recently, however, a group of substances has been brought into use which exert a very marked effect upon the blood pressure. I refer to the nitrites. Their action consists chiefly in producing a dilatation of the peripheral vessels, mainly of the head and neck, and of the vessels of the splanchnic area, causing a marked fall in the blood pressure while the heart is accelerated. The different members of this group vary in regard to the rapidity, the intensity, and the duration of their action. Amyl nitrite acts instantaneously, but only for about five minutes. Nitroglycerin, and in fact all the other nitrites, act less vigorously but much longer. Nitroglycerin acts more quickly and more intensely, but for a slightly shorter period than sodium nitrite. In both the action is well marked in fifteen minutes and lasts for one to two hours. Erythrol tetranitrate acts much more slowly and attains the height of its action in about two hours, but its duration is much longer.

Theoretically, amyl nitrite should be administered at once in the case of hæmoptysis and repeated if necessary in five minutes. Following the first dose nitroglycerin or sodium nitrite should be given, and in a few minutes (twenty to thirty) erythrol tetranitrate should be given. This would insure a lowered pulmonary tension for some time. The great difficulty, however, lies in the fact that it is difficult to tell just when to repeat the dose. It is dangerous to lower the blood pressure too much and dangerous not to lower it enough. To overcome these difficulties I have recently taken the patients' blood pressure[1] every two hours and ordered the doses accordingly, aiming to keep the tension within certain limits. Practically, I use amyl nitrite as suggested, and if the patient is nervous administer morphine (one-eighth grain) hypodermically and along with it nitroglycerin or, which I prefer on account of its greater stability and fewer untoward symptoms, sodium nitrite (one grain). In some cases the patient cannot inhale amyl nitrite, and in these cases the sodium nitrite or nitroglycerin should be given hypodermically, immediately, and repeated as often as necessary. A careful nurse may be quickly trained to take accurate readings of the sphygmomanometer and the cuff may be left upon the arm indefinitely if preferred. To determine at which level to keep the blood pressure I take it several times

[1] The systolic pressure only has been studied.

at short intervals and attempt to keep it usually between "100 and 115 or 120 mm. of mercury." It is comparatively easy to do this with the aid of sodium nitrite.

Hæmoptysis frequently recurs or even occurs in the early morning hours and the patient awakens spitting blood. Howell's theory of sleep offers a striking explanation of this phenomenon. This observer holds that sleep is due to the fatigue of the vasoconstrictor centre (or centres), and he has shown by the plethysmograph that a dilatation of the peripheral vessels occurs during sleep. In the early morning hours, when the vasoconstrictor centre is regaining its lost tone, remarkable vacillations occur in the plethysmographic records, which would indicate considerable variation in the quantity of blood supplied to the right side of the heart and, as we have mentioned before, concomitant variations in the pulmonary blood pressure. Sudden variations in pressure are, in all probability, more dangerous than a steady high pressure. To prevent these variations as much as possible and to equalize the blood pressure, I have recently given morphine and sodium nitrite hypodermically between midnight and 2 A.M., waking the patient if necessary.

Aconite has been suggested in the treatment of hæmoptysis and its use, when controlled in the foregoing manner, may prove to be very beneficial. I would suggest its use in cases complicated with fever.

To recapitulate briefly, I would suggest that the blood pressure be frequently observed, that morphine be used when necessary to quiet the patient and so equalize the blood pressure, that sodium nitrite be exhibited to reduce when necessary the blood pressure, and that in case of a sudden hæmoptysis amyl nitrite be administered at once when possible, to produce a marked fall in the blood pressure and so aid in a temporary cessation, at least, of the hæmoptysis.

In no symptom, or complication, as you wish it, is judgment of the effect of any treatment more difficult than in hæmoptysis. I am fully persuaded that many of our patients recover from hæmoptysis in spite of our treatment. I have had too few cases to hazard anything more than a tentative opinion upon the beneficial effects of this method of treatment. It seems to me, however, a little less empirical than many others and I submit it to you in the hope that any of you who think well enough of it will endeavor to establish its value or to prove its worthlessness.

A NEW INTESTINAL PARASITE OF MAN: PARAMŒBA HOMINIS.

By Charles F. Craig, M.D.,

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Since the brilliant investigations of Schaudinn[1] upon the morphology and method of reproduction of the amœbæ inhabiting the intestine of man were published, in which he demonstrated the existence of at least two species, one harmless and the other pathogenic, the study of these organisms has acquired new interest and importance. In a previous contribution[2] I have described in detail the results of personal work upon Entamœba coli and Entamœba dysenteriæ (histolytica), all of which were confirmatory of Schaudinn's conclusions, and have since been so fortunate, during several months' work in the Philippine Islands, as to be able to study the peculiar amœba which will be described, and which, not only because it is a hitherto undescribed species for man, but on account of its complicated life cycle is of the greatest interest. This parasite is of rare occurrence, as I have observed it in but six cases out of several hundred patients whose feces I have examined. I have only observed it in natives of these Islands, although I have looked very carefully for it in American soldiers and civilians, some of whom have lived for a considerable period of time in the tropics.

Occurrence. This amœba was observed in the feces of six natives who were patients in the hospital at the time the examinations were made. In five of the cases the only symptoms of importance present was a diarrhœa, the stools being of watery consistence, and containing in three of the cases a small amount of blood and mucus. In none of these cases was Entamœba dysenteriæ present. The sixth patient was suffering from a very severe attack of acute amœbic dysentery, and the new amœba was found in small numbers in conjunction with immense numbers of Entamœba dysenteriæ (histolytica). In one case Trichomonas intestinalis was present.

Morphology and Life Cycle. Before describing the morphology of this parasite it will be necessary to sketch briefly its life cycle, for at different periods in the latter the morphology varies very greatly. This amœba, unlike any other hitherto described as infecting man, undergoes a flagellate and an amœboid stage of development, resembling in this the water amœba first described by Schaudinn and named by him Paramœba eilhardi. I have been able, by making repeated examinations, to trace the life cycle of this

[1] Arbeiten aus dem Kaiserlichen Gesundheitsamte, 1903, xix. Heft 3, p. 563.

[2] American Medicine, May 27, June 3 and 10, 1905, vol. ix., Nos. 21, 22, and 23, pp. 854–861, 897–903, 936–942.

amœba in the intestinal contents, and while there are many points in connection with this cycle which require further study, especially as regards the intervals of time which elapse between the various stages of growth, enough has been observed to enable us definitely to place this organism in the same genus with Paramœba eilhardi.

LIFE CYCLE. The new amœba, as I have stated, is a flagellated organism during one stage of its growth, this stage being succeeded by a stage in which the true amœba form is observed. In both these developmental stages reproduction is probably possible, although I have observed it only in the amœboid stage; in this stage reproduction by simple division can be demonstrated (Fig. 1).

FIG. 1

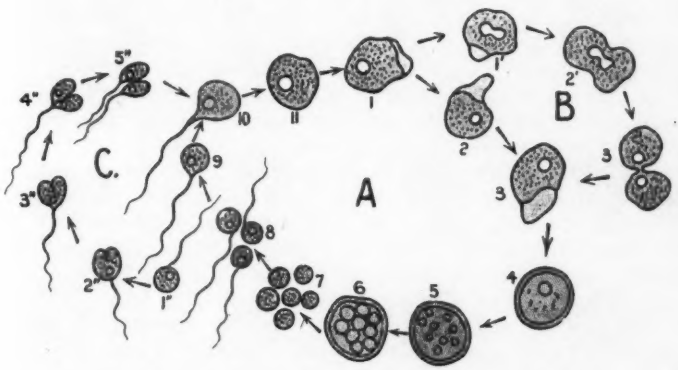


Diagram illustrating the life cycle of Paramœba hominis: *A*, 1 to 11. The entire life cycle, showing the amœba and flagellate stages, which has been observed. *B*, 1 to 3. Cycle of reproduction by simple division, which has been observed. *C*, 1 to 3. Cycle of reproduction, by longitudinal division of the flagellates, which is hypothetical.

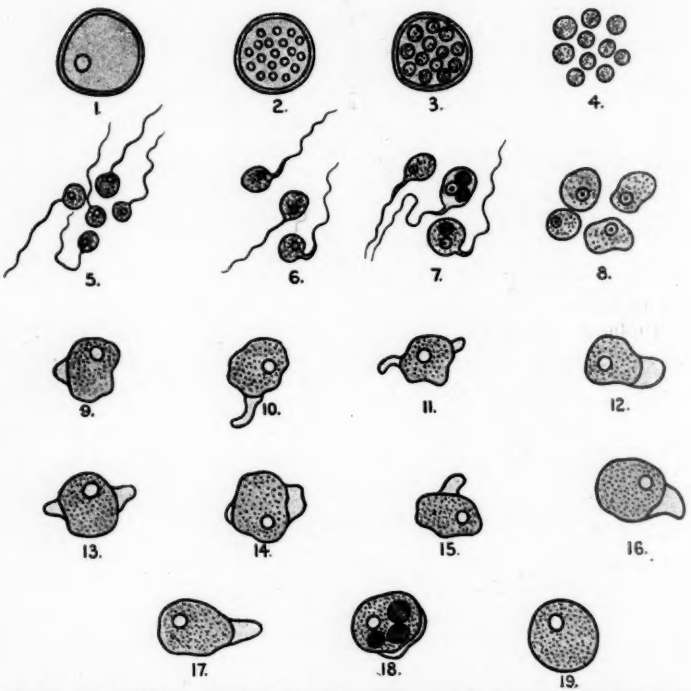
Beginning with the amœboid stage, after the organism has reproduced an unknown period of time by simple division, the amœbæ become circular in shape and there is developed a refractive, hyaline, double outlined cyst wall. Within the cyst so formed a number of small spherical bodies are produced, which are liberated by the rupture of the cyst, and which possess a long, delicate flagellum, and are actively motile. The flagellated organisms increase rapidly in size and eventually become motionless, lose their flagella, and develop into the true amœboid form, after which they undergo reproduction by simple division for a period, and then become encysted, as has been described. Whether the flagellate form reproduces as such, as does Paramœba eilhardi, I have not been able to determine.

MORPHOLOGY. Having thus briefly outlined the life cycle of this organism, the morphology as observed in its various stages of

development may be considered, beginning with the amœbic form at the time of encystment (Fig. 2).

Encysted Stage. At this time the parasite measures from 15 to 20 μ in diameter, and is circular in shape. It appears opaque and

FIG. 2



Various forms of the flagellate, cystic, and amœbic stages in the growth of Paramœba hominis: 1, newly formed cyst, showing membrane and nucleus; 2, cyst showing absence of nucleus and a large number of small refractive dots; 3, cystic form, presenting within the cyst numerous young flagellates; 4, young parasites after liberation from the cyst and before the development of the flagellum; 5, young flagellates after the appearance of the flagellum; 6, older flagellate forms of Paramœba hominis; 7, fully grown flagellate form of Paramœba hominis (note the well-defined nucleus; two of the organisms contain red blood corpuscles); 8, flagellate forms immediately after the disappearance of the flagellum and before the appearance of amœboid motion; 9 to 18, various forms of the amœbic stage of Paramœba hominis (note the well-defined nucleus, the differentiation of the ectoplasm and endoplasm, the blunt pseudopodia, and the granular appearance; in 18 the amœba contains three red blood corpuscles); 19, Paramœba hominis at the termination of its amœbic stage, just previous to encystment.

is of a dull-gray color; no difference can be detected between the ectoplasm and endoplasm, the protoplasm appearing homogeneous; surrounding the organism is a delicate, very refractive capsule, having a double outline. In the earliest stage of encystment a nucleus,

spherical in shape and very small, is generally observed, situated a little to one side of the centre, but this nucleus entirely disappears at a later stage, being replaced by numerous brightly refractive dots which are scattered throughout the protoplasm. In some instances a smaller, oval body may be seen situated a little to one side of the nucleus; this is not so refractive. At a later stage the cyst appears to be crowded with small circular bodies which are undoubtedly the young flagellate organisms. The appearances described are those presented in fresh specimens. I have not been able as yet to stain the cystic forms successfully.

Young Flagellate Stage. While I have not been able to observe the actual rupture of the cyst wall, and the liberation of the young flagellated organisms, in all the cases observed I have found groups of such organisms, lying apparently in cellular detritus, and arranged in circular masses, corresponding in size to the original cyst, although the cyst wall had disappeared. At first these young organisms do not appear flagellated, are very small, measuring from 3 μ to 5 μ in diameter, are circular in shape, and have a finely granular protoplasm in which no nucleus can be demonstrated. After watching these young amœbæ for a while it will be seen that one by one they become motile, a very delicate flagellum appearing at some portion of the periphery; they disengage themselves from the material in which they seem embedded, and move forward in a rapid, jerky way, propelled by the flagellum, which thus appears to be situated posteriorly. It is impossible to stain these young forms distinctively.

Fully Grown Flagellate Stage. The young flagellate forms increase very appreciably in size, and in all the specimens which I have examined, the intermediate stages in the growth could be easily traced, but as the morphology varies but little until the flagellate form has attained its full growth, it is unnecessary to give it in detail.

When fully grown the flagellate forms measure from 10μ to 15μ in diameter and are perfectly circular in shape, save at that portion of the periphery where the flagellum is attached. The latter is three to four times as long as the diameter of the parasite, and tapers very rapidly, the outer three-fourths being so extremely slender that it requires very careful focusing to demonstrate it. At the point of attachment to the body of the parasite the flagellum is continuous with the protoplasm, and the nucleus appears to be situated, in the majority of instances, near this point. The flagellum is situated posteriorly, and the organism moves forward rapidly, propelled by the flagellum, the motion of the latter being lashing in character. The protoplasm is homogeneous in greater part, but small refractive granules are often observed, and a small spherical nucleus, having a well-marked nuclear membrane, is usually present. I have several times observed from one to two red blood corpuscles within

the flagellate form, so that it is apparent that the property of engulfing these cells is not confined to the amœboid stage. As stated I have not been able to observe reproduction in this stage. Stained preparations, even when Wright's stain is employed, are not satisfactory, the organism staining a very dark purple color throughout, and the flagellum does not take the stain.

Young Amœbic Stage. Repeated observations of these fully grown flagellate forms demonstrate that after gradually becoming less motile, progressive motion is lost, and that after lashing around with the flagellum for a while, this also becomes motionless, and disappears, being either drawn within the body of the parasite or degenerating. With the disappearance of the flagellum, amœboid motion commences, appearing at first as an undulatory motion of the border of the parasite, followed by the projection of small, rather pointed pseudopodia. At first there is no progressive motion, the pseudopodia being projected and withdrawn rapidly, but they gradually increase in size and progressive motion begins; the motion is fairly rapid for an amœba, the pseudopodia being bluntly conical in shape, and as soon as they are projected the endoplasm flows rapidly into them. There is a distinct difference in the appearance of the ectoplasm and the endoplasm, the latter being more refractive than the former and much larger in amount. When the organism is motionless the ectoplasm and the endoplasm cannot be differentiated. A nucleus is present, refractive, spherical in form, and presenting a well-defined nuclear membrane. It is always situated in the endoplasm, and changes its position with the movements of the organism. Vacuoles have not been observed. One to two red blood corpuscles are occasionally seen in these young amœbæ. The endoplasm is finely granular in structure.

Fully Grown Amœbic Stage. After becoming amœboid, the parasite increases considerably in size, measuring when fully grown from 15 μ to 25 μ in diameter; the distinction between the ectoplasm and the endoplasm is well-marked when the organism is moving, but invisible when it is motionless; the nucleus is distinct and presents a heavy nuclear membrane; no vacuoles are present, but the endoplasm contains a great deal of granular material and often from one to four red blood corpuscles. When fully grown the motility is very marked and is progressive in character.

In stained specimens no difference can be detected in the staining reactions of the ectoplasm and the endoplasm, but the nucleus stains a brilliant red with Wright's stain, and appears to be composed almost entirely of chromatin.

Precystic Stage. In the amœboid stage I have repeatedly observed reproduction by simple division, but in the same specimen of feces numerous amœboid forms will be observed which are becoming encysted, as well as those in which the process is complete. The manner in which this organism becomes encysted is very interesting.

The amœboid motion gradually ceases and suddenly the organism begins to rotate very rapidly upon its axis, this rotation sometimes lasting for an hour or more.

It is probable that it is during this process of rotation that the cyst wall is formed, for when rotation ceases it is observed that the organism is surrounded by the delicate, double-outlined membrane which has already been described. After rotation has ceased the organism appears slightly smaller than while in the amœboid stage, and the nucleus is shrunken and in some instances is not distinguishable.

Classification. It is evident that the parasite described passes through an amœbic and a flagellate stage of development, and for this reason it cannot be placed in the genus Entamœba. The organism might be regarded as a connecting link between the amœbæ proper and the flagellates, but as Schaudinn has already described a very similar organism, occurring in water, and has placed it in the genus Paramœba, I am of the opinion that this new amœba of man should be placed in the same genus. While I have not been able to demonstrate reproduction by longitudinal division during the flagellate stage of growth, which occurs in Paramœba eilhardi, it is very probable that such a mode of reproduction occurs, for the other developmental stages of the new parasite are identical with those of Paramœba eilhardi.

For these reasons I believe that this organism may be properly placed in the genus Paramœba described by Schaudinn, and would suggest that the name Paramœba hominis be given this new intestinal parasite of man.

Pathogenicity. As to whether Paramœba hominis produces any pathological condition of the intestine, or whether it is a harmless amœba, as is Entamœba coli, I am not prepared to say. In all the cases but one in which it was observed its presence was accompanied by the usual symptoms of a severe diarrhœa, and it was the only animal organism present which could be looked upon as being of any etiological significance. In the one case it occurred in conjunction with Entamœba dysenteriæ, and, therefore, it is impossible to say what part Paramœba hominis played in the infection.

Differential Diagnosis. There is but one intestinal parasite which might be mistaken for Paramœba hominis, because of certain peculiarities in its development. I refer to Trichomonas intestinalis. The latter organism is often observed in the resting stage, when it is circular in form, and appears to possess very limited amœboid motility. It is much smaller than Paramœba hominis at the beginning of the amœboid stage, and it does not possess active progressive amœboid motion, as does the latter. In the flagellate stage Paramœba hominis is distinguished from the trichomonads by the absence of the undulating membrane and the presence of one flagellum, as well as by its circular shape. It is impossible to confuse it with

the cercomonads, as it does not resemble these organisms in the least. It would be somewhat difficult for one who has not traced the development of Paramœba hominis to distinguish its amœbic stage from that of Entamœba coli, but the presence in the same specimen of cystic forms, rotating forms, and various stages of the flagellate form makes the diagnosis of Paramœba hominis easy. In conclusion, I would call attention to the fact that this parasite has been found only in natives of the Philippine Islands, but that in all probability further research will show that it is much more frequently present than appears to be the case at present.

THE ACETONE BODIES: THEIR OCCURRENCE AND SIGNIFICANCE IN DIABETES AND OTHER CONDITIONS.

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As our knowledge of the so-called acetone bodies, that is, acetone, diacetic acid, and β-oxybutyric acid, increases they assume a growing importance and interest in their connection with many pathological conditions. As symptoms of disordered metabolism they are of significant value. Their presence in diabetes and febrile conditions has been recognized for a considerable time. Their more recent discovery in operative procedures, pregnancy, digestive disturbances, nervous disorders, malignant disease, and various forms of poisoning has made them of interest to an ever-increasing number of the medical profession.

The graphic formulæ of the acetone bodies at once indicates to us their close relationship.

β-oxybutyric acid.	Aceto-acetic acid (diacetic acid).	Acetone.
CH_3	CH_3	CH_3
|	|	|
CHOH	CO	CO
|	|	|
CH_2	CH_2	CH_3
|	|	
COOH	COOH	

By oxidizing β-oxybutyric acid we obtain diacetic acid:

$$CH_3\text{-}CHOH\text{-}CH_2\text{-}COOH + O = CH_3\text{-}CO\text{-}CH_2\text{-}COOH + H_2O,$$

and when diacetic acid is heated to 100° C. it is easily decomposed into acetone and carbonic acid:

$$CH_3\text{-}CO\text{-}CH_2\text{-}COOH = CH_3\text{-}CO\text{-}CH_3 + CO_2.$$

The latter reaction occurs so readily that hitherto no satisfactory method has been devised of separating the acetone and diacetic acid of the urine, and, therefore, all quantitative estimations of acetone represent the combined output of diacetic acid and acetone. We are able, however, to estimate separately the amount of β-oxybutyric acid and the combined amount of acetone and diacetic acid.

The relationship of the acetone bodies is further made evident by the order in which they make their appearance in the urine in various pathological conditions. In a severe case of diabetes, for instance, the first of these bodies which we find is acetone, indicating that the organism is beginning to show its failing powers of oxidation; if this process advances we next detect diacetic acid, and when this has become evident in increasing amounts oxybutyric acid will finally be found, thus pointing out the increasing imperfection of oxidation. When the diabetic begins to improve the oxybutyric acid is the first to disappear, followed by diacetic acid, and lastly by acetone, but always in this sequence—thus indicating in a graded manner the increasing capability of the organization to carry out its normal processes of oxidation.

It seems to be pretty conclusively proved that β-oxybutyric acid is the antecedent body from which diacetic acid and acetone are formed. Schwartz (*Archiv f. exp. Path. u. Pharm.*, 1898, Band xxxx.) has given diacetic acid by the mouth to diabetic animals and has seen a partial conversion into acetone in the urine. Geelmuyden (*Skand. Arch. f. Phys.*, 1901, Band xi.) has given sodium salts of diacetic acid to normal men, who were on a mixed diet and a diet without carbohydrates, and found an increase in the acetone output in each instance. It is not improper, however, in connection with these experiments to emphasize the fact that as regards the acetone bodies the metabolism of animals is very different from the metabolism of man; hence, conclusions from animal experimentation must be drawn with extreme caution. In this work in many instances the results obtained in animals have been found to be utterly different from those obtained in man in corresponding experiments.

It has been claimed by Arnold (*Zentralbl. f. inn. Med.*, 1900, p. 423) that the acetone of the urine is excreted as diacetic acid and is converted into acetone in the urine. It seems to me, on the contrary, that there is considerable evidence that acetone as such is excreted and may occur entirely independent of the excretion of diacetic acid. In a number of my own cases I have been able to detect and estimate the quantity of acetone in the urine without being able to detect diacetic acid by either Gerhardt's or Arnold's reactions, the latter being the most delicate reaction for diacetic acid which we possess. The following table shows a number of such instances:

CASES SHOWING PRESENCE OF ACETONE WITHOUT DIACETIC ACID.

Case.	Date of examination.	Diagnosis.	Acetone.		Test for diacetic acid.			
			Lieben's test.	Quantity in grams.	Arnold's.	Gerhardt's.	Diazo.	Riegler's
E. W.	April 14, '05	Cycle vomiting	+	..	0	0	0	0
L. B.	May 16, '05	Diabetes	+	..	0	0	0	
	June 9, '05	Diabetes	+	0.220	0	0	0	0
A. C.	April 12, '05	Diabetes	+	..	0	0	0	
B. B.	April 13, '05	Diabetes	+	..	0	0	0	
E. A. S.	April 15, '05	Diabetes	+	..	0	0	0	
C. C. K.	April 15, '05	Diabetes	+	..	0	0	0	0
	May 25, '05	Diabetes	+	0.018	0	0	0	
L. H.	June 7, '05	Diabetes	+	0.021	0	0		
M. E. M.	May 9, '05	Diabetes	+	0.017	0	0	0	0

Further, as regards Arnold's contention it may be said that in diabetes and other conditions a large amount of acetone is found in the breath, and diacetic acid is not found in the expired air; therefore, it would seem probable that acetone is present as such in the circulating blood.

However, when acetone appears in any considerable amount in the urine, diacetic acid can always be detected, and when in turn diacetic acid is evident in large quantities, as for example when we have an exceedingly strong Gerhardt reaction, oxybutyric acid is always found.

TABLE SHOWING APPEARANCE OF DIACETIC ACID WHEN ACETONE IS EXCRETED IN CONSIDERABLE QUANTITIES.

Case.	Date of examination.	Diagnosis.	Acetone tests.		Diacetic acid tests.				Amount of acetone in twenty-four hours, grams.	Rotation.	
			Lieben's.	Legal's.	Arnold's.	Gerhardt's.	Diazo.	Riegler's.		Before fermentation.	After fermentation, indicating presence of oxybutyric acid.
C. C. K.	May 25, '05	Diabetes	+	0	0	0		..	0.018		
M. E. M.	May 9, '05	Diabetes	+	0	0	0		0	0 017		
L. H.	June 7, '05	Diabetes	+	?	0	0		..	0.021x		
B. B.	April 25, '05	Diabetes	+	+	-	0		..	0.037x		
C. C. K.	April 27, '05	Diabetes	+	-	?	..		..	0 060		
L. B.	May 10, '05	Diabetes	+	+	+	0	0	0	0 068		
C. C. K.	June 13, '05	Diabetes	+	-	-	0	0	0	0.399		
F. J. M.	June 8, '05	Diabetes	+	+	+	-	-	..	0.160x		
L. B.	June 9, '05	Diabetes	+	+	0	0	0	0	0.317		
G. L.	May 1, '05	Diabetes	+	+	+	+	+	..	0.800		
S. C.	May 5, '05	Diabetes	+	+	+	+	+	..	0.616		
G. L.	May 15, '05	Diabetes	+	+	+	+	+	?	0.657		
G. L.	June 5, '05	Diabetes	+	+	+	+	+	?	1.113		
S. B. C.	May 3, '05	Diabetes	+	+	+	+	+	..	1.111x		
G. L.	May 8, '05	Diabetes	+	+	+	+	+	+	1.333x	+0.5	-1.2
J. F.	Feb. 12, '04	Diabetes	+	+	+	+	+	+	0.292	+6.0	-1.0
J. F.	Feb. 22, '04	Diabetes	+	+	+	+	..	..	0.962	+6.8	-0.4

+ = positive reaction. - = weak reaction. ? = doubtful reaction. 0 = negative reaction. x = amount in litre.

I think we may look upon the excretion of β-oxybutyric acid and diacetic acid as invariably due to pathological conditions, while the appearance of any considerable amount of acetone must be regarded in the same light. However, small amounts of acetone may be found in the urines of apparently perfectly healthy individuals. Von Jaksch (*Ueber Acetonurie u. Diacetonurie*, Berlin, 1895) found in normal men a urinary acetone excretion of 0.010 gram per day, and v. Engel (*Zeit. f. klin. Med.*, 1892, 20) puts the normal limits at from 0.006 to 0.018 gram of acetone a day. Most investigators claim that in normal subjects acetone is given out in the breath in infinitesimal quantities, but in pathological conditions more acetone may be found in the expired air than in the urine. Schwartz (*Verhdlgn. d. 18 Kongr. f. inn. Med.*, 1900) claims that 70 per cent. of the acetone may be excreted in the breath. Geelmuyden (*Zeitsch. f. physiol. Chem.*, 1897, Band xxiii.) has estimated that at times 80 to 95 per cent. of the acetone may be lost through the lungs. There seems to be no constant ratio between the amount of acetone excreted by the kidneys and the lungs. In pathological conditions, if the urinary acetone is increased and at another time diminished, the total acetone excretion may be constant, on account of the variability of the acetone of the expired air. In starvation experiments the urine may contain acetone, diacetic and β-oxybutyric acids, while acetone is found in considerable quantities in the breath. The acetone bodies are found in considerable quantities in certain digestive disturbances, and in many febrile diseases, such as the exanthemata, pneumonia, typhoid fever, etc. Acetone has not been found in the blood of normal men, but v. Jaksch found it in the blood in febrile cases; and in a diabetic Magnus-Levy (*Arch. f. exp. Path. u. Pharm.*, 1899, Band xlii.) found 0.1 to 0.3 per cent. of acetone in the blood. In pathological conditions acetone has been detected in the sweat and in the saliva.

Waldvogel (*Die Acetonkörper*, Stuttgart, 1903, p. 110) gives a list of the drugs which are known to increase acetone production; among them are benzol, benzonaphthol, antipyrin, morphine, and heroin. Acetonuria has been described by various authors as following poisoning with phosphorus, phloridzin, atropine, coal gas, curare, and lead. In some of these the cause may be found in the attendant starvation, vomiting, or other gastrointestinal disturbances.

Marro (quoted by Waldvogel, *Die Acetonkörper*, p. 108) claims that nervous shock and excitement can lead to an increased production of acetone bodies. He experimented by keeping a dog in a state of terror for eight hours and then could estimate a marked increase of acetone. It is a well-recognized fact that nervous excitement is bad for diabetics and may be the inciting cause of coma.

The acetone bodies have been detected in considerable amounts before and after operations. It is probable that this is largely due to

the restricted diet, nervousness, and vomiting, and not as many have supposed to the administration of the anæsthetic.

It was thought at one time that an acetonuria in a pregnant woman was an indication of a dead fœtus, but recent more extensive observations on acetone excretion before, during, and after labor have led to a modification of this view.

It is in diabetes that the excretion of acetone, diacetic and oxybutyric acids makes itself most evident and reaches its maximum. Magnus-Levy (*Arch. f. exp. Path. u. Pharm.*, 1899, Band xlii.) estimated in a case of diabetes a twenty-four-hour excretion of 19 grams of acetone, and in a case of diabetic coma, Naunyn found (Nothnagel, *Spec. Path. u. Ther.*, 1900, Band vii., 1, p. 185) an output of 188 grams of sodium β-oxybutyric acid in a single day.

An effort has been made, hitherto without success, to determine the particular organ of the body in which the acetone bodies are manufactured. In a diabetic subject, dying in coma, Hugounenq (*Compt. rend. Soc. Biol.*, 1887) found a considerable amount of oxybutyric acid in the blood; in a similar case Magnus-Levy (*Archiv. f. exp. Path. u. Pharm.*, 1899, Band xlii.) isolated oxybutyric acid from the liver, spleen, muscles, blood, and stomach contents. Never, however, have acetone bodies been found in such amounts, in any particular organ, that their presence there could not be accounted for by the amount which might be brought to them by the circulating blood. A number of students of this subject, among whom perhaps Müller (*Verhandlun. d. Kongr. f. inn. Med.*, 1898) is the most ardent, regard the alimentary tract as the chief source of acetone-body production. They base their views mainly on the increase of acetone bodies in gastrointestinal disturbances, on the rapid action of carbohydrates when administered by the mouth in reducing the acetone formation, its failure to accomplish this result when given by the rectum, and the constant amount of sugar in the blood during starvation when the acetone bodies are notably increased. The preponderance of evidence seems to be against this theory. The clearing out of the alimentary tract by purgatives usually leads to a diminished output in an established acetonuria; in the stomach and intestinal contents these substances are never present in greater amount than in other organs; in fact, Magnus-Levy and Geelmuyden have found the amount less than in other organs in diabetic coma; in many gastrointestinal disturbances acetone bodies cannot be recovered from the urine, feces, or stomach contents. As was shown in the case of the famous faster Cetti, there is no parallelism between proteid destruction and acetone-body formation, which one would expect if there were a direct relationship between proteid decomposition and acetone production (Satta, *Beiträg. zur chem. Phys. u. Path.*, 1904 and 1905, vi., p. 390). Starvation acetonuria is a direct argument against the alimentary tract as its source, the large amount of these substances found in starvation and in subjects of diabetic

coma who are unable to take food, drives us to some other explanation of the source of acetone-body production.

It seems most probable that any part of the body which fails in the proper oxidation of the foodstuffs brought to it may be a source of acetone-body production.

The question next arises as to what is the antecedent material which failing to be oxidized completely in the various organs and tissues of the body results in the production of acetone, diacetic and oxybutyric acids. At various periods this role has been ascribed to proteids, carbohydrates, and fats, each in their turn. In the laboratory, by purely chemical agencies, acetone bodies have been obtained from each one of these foods. At present the evidence strongly indicates the abnormal destruction of fat as the source of excessive acetone-body formation.

The theory of the proteid origin of acetone bodies meets with many difficulties. There is no parallelism between the amounts of proteid destruction, as represented by the output of nitrogen, phosphates, and sulphates, and the amount of acetone bodies excreted. This has been pointed out by many observers in conditions of starvation and diabetes. Von Noorden (*Lehr. d. Path. d. Stoffuec.*, Berlin, 1893, p. 178) observed a patient on a reduction cure who daily converted 180 grams of proteid, but lost no weight, and excreted only a trace of acetone. Magnus-Levy (*Archiv f. exp. Path. u. Pharm.*, 42 u. 45) reports a case in which there was a metabolism of 262 grams of proteid in three days, out of which amount of proteid, at most, only an equal amount of oxybutyric acid could be made, and yet this patient excreted 342 grams of oxybutyric acid in this period. It is true that a patient on an exclusive proteid diet will produce considerable amounts of acetone, but it seems probable that this is due to the unusual destruction of body fat. Again, the administration of proteid food to a starving man reduces the amount of acetone excretion. This is probably due to its power to save fat destruction and also the influence of the carbohydrate moiety of the proteid which assists in the more complete oxidation of the acetone bodies.

As regards carbohydrates, their withdrawal from the diet of normal man is almost invariably followed by an increase in the acetone output and their administration results in a reduction of the acetone excretion. In many observations on diabetics a similar relationship has been demonstrated. It would not, therefore, seem possible that carbohydrates can be the source of the acetone bodies.

When we come to consider fats as a source of the acetone bodies the evidence is much better. There is a distinct parallelism between the amount of fat broken down and the amount of acetone bodies excreted. Loeb and Mohr (*Zentralb. f. Stoffuec. u. Verdkrankh.*, 1902) in a case of diabetes found that the amount of oxybutyric acid varied directly with the amount of fat in the food. Waldvogel

(*Die Acetonkörper*, p. 82) has found that by feeding fat in cases of diabetes, in starvation, and in those who for some time had been on an exclusive fat-proteid diet, the acetone output was notably increased. The administration of large quantities of fat to healthy subjects on a mixed diet is asserted by Schwartz (*Deutsch. Archiv. f. klin. Med.*, 1903, lxxvi.), Geelmuyden (*Zeit. f. phys. Chem.*, 1897, xxiii.), Schumann-Leclerq (*Dublin Journal of Med. Sci.*, September, 1901), and others to cause an increase in the excretion of acetone.

Starvation experiments on healthy men afford us considerable insight into the conditions necessary for the production of the acetone bodies. Mere deficiency in the caloric values of food is not sufficient to cause the appearance of an abnormal amount of acetone; for example, a man observed by Waldvogel (*Die Acetonkörper*, p. 117) took only 1.4 litres of beer and 750 grams of bread, without the appearance of acetone, and Rosenfeld (*Centralb. f. inn. Med.*, 1895, xvi.) reports a man who ate only 125 grams of cane sugar in twenty-four hours, with no increase in his acetone excretion. Total starvation may cause acetone production and an excretion of something less than one gram in twenty-four hours. A pure proteid diet in a healthy man may cause the excretion of considerable amounts of acetone but less than total starvation; in this case the acetone probably has its origin in the body fat. A pure fat diet may produce acetone values as great or greater than starvation. The extent of acetone excretion, as has been shown by Joslin (*Journ. Med. Research*, October, 1904, xii., No. 3), depends on the capability of the fat for absorption, hence on the character of the fat employed. A proteid-fat diet may produce acetone values approaching those of total starvation; here the source of the acetone is probably the fat both of the food and of the body. The addition of carbohydrates to any of the above diets at once reduces the acetone output; the rapidity of this action depends on the rapidity of the absorption of the carbohydrates and hence to a considerable degree upon the kind of carbohydrates employed. These facts may be tabulated, as follows:

EXPERIMENTS ON HEALTHY MEN.

No.	*Diet.*	*Amount of acetone.*	*Probable source.*
I.	Starvation.	Up to one gram in twenty-four hours.	Body fat.
II.	Exclusive fat.	More than I (usually).	Body and food fat.
III.	Exclusive proteid.	Less than I.	Body fat.
IV.	Proteid-fat.	About equal to I.	Body and food fat.
V.	Exclusive carbohydrate.	None.	
VI.	Carbohydrates and fat.	None.	
VII.	Carbohydrates and proteid.	None.	
VIII.	Carbohydrates and fat and proteid.	None.	

There has been considerable speculation as to the manner in which the introduction of carbohydrates acts in reducing the output of the acetone bodies. One of the very noticeable features of the reduction of this acetone output by carbohydrate introduction is the extreme rapidity of its action. The very suddenness of this in itself indicates that the first effect must be to furnish the conditions necessary for the complete oxidation of the acetone bodies at that time circulating in the blood. This is followed by a diminution in the destruction of body fat.

The difference in various carbohydrates in reducing an acetonuria has been shown by Jorns (*Inaug. Diss.*, Würzburg, 1903). After inducing an acetonuria in himself by a period of starvation he ate definite amounts of various kinds of carbohydrates; the greatest effect in diminishing the acetone was produced by the ingestion of cane sugar, followed in order by grape sugar, glycuronic acid, and starch. This is probably due to the varying absorbability of the different substances. Satta has noted a marked reduction in starvation and diabetic acetonuria following the administration of levulose and galactose.

Other substances which interfere with the production of the acetone bodies are glycerin, lactic and tartaric acids, and glycocol. These may act directly, or may be changed into sugar by a synthetic process.

ACETONE BODIES IN DIABETES.

The study of the acetone bodies in diabetes is not only of extreme scientific interest, but also has a most important bearing on the therapeutic measures to be employed. As has been previously pointed out the amounts of these bodies excreted reaches a greater total in diabetes than in any other known conditions. The relative amounts of acetone, diacetic and oxybutyric acids may vary extremely in various stages of the disease. In the early stages acetone is the first of these bodies to be excreted. Later diacetic acid appears, followed by the excretion of β-oxybutyric acid. In the advanced stages of the disease, when oxybutyric acid is excreted in enormous amounts, the acetone may appear in comparatively small quantities. This change is due to a gradual decreasing power of oxidation of the body cells or their products. When it is possible to improve the metabolism the acetone bodies disappear in the inverse order in which they were discovered.

The ratio between the acetone of the urine and that of the breath in diabetes is not constant. As a rule in mild diabetes the acetone of the breath is relatively greater, in severe cases the acetonuria usually predominates. This may be explained by the fact that in the severe cases β-oxybutyric and diacetic acids are manufactured

and can only be excreted by the kidneys, and in the urine the diacetic acid is estimated as acetone, while in the cases in which acetone alone is made, this is readily excreted by both lungs and kidneys. Moreover, in the very severe cases of diabetes the body is unable to oxidize its diacetic and oxybutyric acids to acetone, and comparatively little of the latter is manufactured. In diabetes there is no parallelism between the amounts of sugar and acetone bodies.

The main source of acetone bodies in diabetes is the imperfect metabolism of fat, which may be the fat of the food or the body fat. As a rule the addition of carbohydrates to the diet results in a diminution of the acetone output; its withdrawal increases the acetone excretion. This is more evident in mild cases; among the very serious cases there are many exceptions reported. It seems to be evident that when the capability of oxidation of the body is not too much out of order, the presence of a certain amount of carbohydrate aids in the oxidation process and protects from destruction the fat which we believe to be the main source of the acetone. Fat feeding, however, seems to be a frequent occasion for the increase of the acetone bodies. This has been conclusively demonstrated by Schwartz (*Deutsch. Archiv f. klin. Med.*, 1903, No. 76) and others.

The loss of power of oxidation in the diabetic has been shown by Waldvogel (*Die Acetonkörper*, Stuttgart, 1903, p. 236). When he injected β-oxybutyric acid subcutaneously in cases of mild diabetes the output of acetone was considerably greater than in similar control experiments on healthy men.

Fever in the diabetic usually reduces the output of sugar and increases the excretion of the acetone bodies, but the usual custom of a change of diet in febrile conditions may possibly account for some observations made in such cases. A similar relationship has been shown to occur just before coma, with a terminal pneumonia (Dreschfeld, *Brit. Med. Journ.*, August 21, 1886). Narcosis seems to have the same tendency, and a fatal coma has been reported in such cases by Hoffa (*Münch. med. Woch.*, 1888) and Futte (*Deutsch. med. Woch.*, 1903).

In coma oxybutyric acid is always present, acetone and diacetic acid may be relatively diminished, and sugar absent; this is probably due to the inability to take food or to utilize that which is taken; the powers of oxidation of the organism have fallen to such a degree that oxybutyric acid is no longer converted into diacetic acid or acetone.

A diabetic may excrete oxybutyric acid for a long time before the fatal issue. Von Noorden (*Die Zuckerkrankheit*, Berlin, 1898) observed such a case for two and one-half years; Weintrands (*Arch. f. exp. Path. u. Pharm.*, 1894, Band xxxiv.) reports a patient who excreted all three acetone bodies for a period of four years before death. I have two patients at present under observation, both of whom showed oxybutyric acid in the urine over two years ago.

It has been customary to regard diabetes as a disease characterized by a failure of the organism properly to utilize the carbohydrates. It seems to me that with our present knowledge we should take a broader view and include in our definition a failure of the organism properly to utilize fats. In every advanced case of diabetes we find an excretion of the acetone bodies, that is to say, the diabetic is unable to utilize fats properly. It is true that the failure to assimilate carbohydrates usually results in a disturbance in the metabolism of fat, hence some might look upon the disorders of fat metabolism in the diabetic as a secondary result of his inability to assimilate carbohydrates; but I believe it is more than this, and that there is a direct perversion of the metabolism of fat comparable to the well-recognized perversion in the metabolism of carbohydrates. In health the very insignificant quantities of carbohydrates will serve to abolish the production of acetone bodies; in certain cases of diabetes, on the other hand, even when a considerable amount of carbohydrates can be utilized, acetone bodies are excreted in spite of the addition of carbohydrates to the diet. In normal man, while acetone bodies are excreted when they are at first put on a proteid-fat diet, the abnormal products of metabolism disappear as the organism in time adapts itself to the new conditions. This has been proved experimentally, and is also illustrated by the fact that the Esquimaux, who subsist almost entirely on fat and proteids, do not have acetonuria. Furthermore, in the carnivora, *e. g.*, a healthy dog, it is almost impossible to produce acetonuria. In severe diabetes, on the other hand, the organism seems to be unable to adapt itself to a diet thus limited, and acetone bodies continue to be excreted.

Is it not then a truer and broader view to look upon progressive diabetes as a disease characterized by a failure to oxidize both carbohydrates and fats?

PRACTICAL SIGNIFICANCE OF ACETONE BODIES.

The recognition of the acetone bodies is of great practical value. If produced in any considerable quantity they are positive evidence of improper metabolism. They are not only of value as an important diagnostic and prognostic sign, but are also a material aid in keeping track of the change in the patient's condition from day to day, and in estimating the value of the therapeutic measures employed. Investigation of the acetone bodies in the urine should be found useful in the study of the dietary of institutions; here the utilization of Legal's reaction is simple and delicate enough to indicate, if found positive in a large number of inmates, that the dietary is insufficient.

To the alienist the detection of acetone may be evidence of a starvation which has been suspected.

In establishing starvation as a cause of death, the presence of acetone and diacetic acid in the urine would be strongly corroborative.

The prognosis of all chronic diseases associated with tissue destruction is more serious if there is a constant acetonuria. For example, in malignant disease the lack of utilization of the food and the destruction of body fat will often thus make itself evident.

Urinary examinations before and after operations and confinement ought to include a test for the acetone bodies.

If a diabetic should put himself on a diet free from carbohydrates in order to obtain life insurance, the examiner might suspect this if an acetonuria were detected, and further tests could readily be made to decide whether he had to deal with a diabetic.

In following a case of diabetes observations on the acetone-body excretion are as important as a knowledge of the sugar output. As soon as diacetic acid appears in the urine, however small may be the amount of glucose excreted, we should recognize that an extensive and improper fat metabolism is in progress. The appearance of oxybutyric acid heralds the fact that the cells of the organism are burning its fuel even less well, that a condition of acid intoxication is imminent, and that coma, however remote, may threaten at any moment.

It would be greatly to our advantage if at a comparatively early stage we could apply some less tedious and complicated test of the powers of oxidation of the diabetic, than the laborious method of long-continued modifications of the diet. This Waldvogel (*Die Acetonkörper*, Stuttgart, 1903, p. 271) has proposed to do, by giving the patient subcutaneous injections of sodium β-oxybutyric acid and thus ascertaining how completely he is able to oxidize a given quantity. It is easy to recognize some possible dangers in a procedure of this kind, and I have hesitated to employ it.

PROPHYLAXIS AND THERAPEUTICS.

The question finally presents itself as to what, in view of our present knowledge, we can do to prevent the formation of acetone bodies and to ward off the injurious effects of their presence. We have seen that nervous irritation, excitement, hunger, and fever favor the production of these poisons. All these should be avoided as far as possible. If operative procedure is necessary in a patient with acetonuria, local anæsthesia should be used, if feasible; if a general anæsthetic must be employed, starving before and after the operation should be reduced to the minimum; if vomiting follows, bicarbonate of sodium and hot lemonade made with sugar should be given by

the mouth or the rectum. Similar rules should be applied in confinement cases.

In febrile conditions, particularly in the diabetic, the diet should include a certain amount of easily absorbed carbohydrates, and every effort should be made by baths and other simple measures to reduce the temperature.

In the diabetic if the withdrawal of carbohydrates is indicated one should do so gradually, allowing the patient time to accustom himself to the change, at the same time watching the amount of fat that can be used with impunity. In a mild diabetic one need not fear the increase of acetone which appears immediately after the withdrawal of carbohydrate food; this occurs in the healthy individual, but one should beware if a large amount of acetone is persistently excreted when the patient has had time to get used to the new diet.

There is at present considerable difference of opinion as to the effect of various kinds of fat on the excretion of the acetone bodies, but the weight of evidence indicates those fats containing the lower fatty acids to be the ones which increase most markedly the production of acetone bodies. Accordingly in selecting our fatty foods we should select, as far as possible, those containing only the higher fatty acids.

If in spite of our efforts we have been unsuccessful in checking the production of diacetic and oxybutyric acids we must resort to the administration of alkalies with the hope of neutralizing them and rendering them less harmful. At the same time we should attempt to aid their more complete oxidation by giving easily oxidizable carbohydrates, for which purpose cane sugar in solution seems to act best. It should be given by the mouth; if coma makes swallowing impossible, a stomach tube or nasal catheter may be used.

Large amounts of water by the mouth, hypodermoclysis, and continuous irrigation of the colon may serve to dilute the poisons and stimulate the kidneys to assist in their rapid removal from the circulating blood. In coma bleeding may be found of service.

THE RELATIONS OF CHRONIC VILLOUS POLYARTHRITIS TO THE DUMB-BELL SHAPED BACILLI.

By Professor Max Schueller,
of Berlin.

Roades Fayerweather, in an interesting article entitled, "Infectious Arthritis, a Bacteriological Contribution to the Differentiation of the Rheumatic Affections," which appeared in The American Journal of the Medical Sciences, December, 1905, referred to my distinction of articular inflammations according to, or

corresponding with, bacteriological, anatomico-pathological, and clinical observations and studies, which distinction I had planned first in the year 1897 and completed later on.

Dr. Fayerweather partly confirmed me in my descriptions, but to some extent he does not interpret my views correctly. The erroneous statements of Dr. Fayerweather I cannot leave undisputed, since I am the one who has advanced the new point of view in classifying diseases of joints.

First of all I cannot agree with Dr. Fayerweather when he applies the too insignificant term "infectious arthritis" instead of my own designation "polyarthritis chronica villosa (bacillaris)," for which latter name I have given scientific reasons. Some of Fayerweather's errors are due to the fact that he has drawn conclusions from his own observations made on comparatively scanty material, and has not taken into consideration the result of my investigations, for which I had a hundred times as much material at my disposal to make cultures. It is apparent that Fayerweather does not know all my publications on this subject, nor my writings on diseases of the joints in general. Concluding his article, Dr. Fayerweather invites further researches on the bacteriology of the articular affections under consideration, and in this I concur with him. I wish, however, to call attention to the scientific standpoint on the broader basis given in my own work on *Diseases of the Joints*, the significance of which for the topic will be readily understood.

As long as twenty-eight years ago—I was at that time clinical assistant and collaborator of Professor Carl Hueter, and we had a very large number of cases of joint diseases at the surgical clinic at Greifswald—I was led to make numerous clinical, pathological, anatomical, and bacteriological investigations of these diseases, and to experiment on animals in order to study the causes, the origin of the different forms of arthritic inflammations. The researches were published in different journals and formed also part of my book: *Experimentelle und histologische Untersuchungen über die Entstehung und Ursachen der skrophulösen und tuberkulösen Gelenkleiden, nebst Studien über die tuberkulöse Infektion und therapeutischen Versuchen.*

Since my removal to the University of Berlin I have studied several years, with Professor Rudolf Virchow's kind consent, in the Berlin Pathological Institute, a very large number of bodies, especially the joints, for different joint diseases, anatomically, histologically, as well as pathologically. My results were published at intervals in medical journals, in papers read in scientific sessions, among others before the Congress of German Surgeons in the year 1884. Again at that time I experimented on animals by inoculating cultures of different micro-organisms, especially such taken from metastatic inflammations of puerperal fever, but also from otherwise diseased joints. Not only by these studies, but more so by constantly increasing

clinical observations—in the average during the year from 500 to 600 patients afflicted with joint disease were treated by me in private clinical and astyclinical[1] practice—I became convinced that the existing classifications of articular inflammations of Volkmann, Hueter, and the English and French authorities were untenable. Some of these old classifications were made on the basis of anatomical changes; some surgeons had been quite arbitrary in classifying, some illogical in considering accidental causes; altogether they were unsatisfactory in every direction from a scientific and practical point of view.

For this reason I made the attempt to group the inflammations of the joints more correctly and more practically, comprising always the etiological moments, the pathologico-anatomical changes, and the most important clinical symptoms. According to these leading points of view I considered in my book, *Die Pathologie und Therapie der Gelenkentzundungen*, published in the year 1887, under the following head groups:

1. Simple acute serous arthritis;
2. Simple chronic serous arthritis (hydrarthron);
3. Suppurative arthritis; suppuration of joints;
4. Arthritis in acute infectious diseases, "metastatic arthritis;"
5. The rheumatic arthritis: (*a*) acute articular rheumatism; (*b*) chronic rheumatic monoarticular inflammation; (*c*) chronic rheumatic polyarticular inflammation;
6. Senile arthritis;
7. Arthritis deformans;
8. Gouty arthritis: (*a*) acute; (*b*) chronic;
9. Syphilitic arthritis: (*a*) in the secondary, (*b*) in the tertiary period, (*c*) in hereditary syphilis;
10. Tuberculous arthritis;
11. Neuropathic arthritis.

I defined and characterized every group as distinctly and precisely as possible, in order to enable us to arrive at a clinical diagnosis of every form of arthritis, and to establish therapeutic rules corresponding with etiological conditions, the most important anatomico-pathological changes, and the clinical symptoms.

My own observations and studies of a great many cases in private, clinical, and astyclinical practice, on the one hand, and the confusion existing and manifested in public discussions among the internal clinicians and spa physicians in regard to the conception and designation of diseases of the joints, on the other hand, induced me to establish a clearer discrimination of what is understood by rheumatic processes in the joints, sometimes attributed to rheumatism in the joints, sometimes called arthritis deformans, sometimes confounded with gout.

[1] Not policlinical nor polyclinical, because both these names are wrong, according to Rose.

In the year 1892 I discovered a peculiar, very small, plump bacillus in the tissues of some joints filled with villous excrescences; because of its peculiar shape I gave it the name dumb-bell bacillus. Characteristic were in such cases the clinical symptoms, the anatomico-pathological peculiarities, the presence of multiple or many villous excrescences on the whole inner surface of the synovialis, the typical structure of proliferating endothelial cell groups *surrounding numerous small vessels*, and differing from those in tuberculous tissue, and the presence of many dumb-bell shaped bacilli between and in the cells of the newly grown hyperplastic tissues of the synovialis and the villous excrescences. The additional fact that I had succeeded by experimenting in causing the same villous process on the synovialis in joints of animals by means of injections of pure cultures of the dumb-bell bacilli, while many other experiments made by me with other bacteria had never resulted in villous excrescences; in short, all these clinical and bacteriological reasons determined me to distinguish between this form and other forms of arthritis and to describe it as chronic villous bacillary inflammation.

We have, it is true, villous excrescences in other forms: for instance, in arthritis deformans, sometimes in syphilitic and sometimes in neuropathic arthritis, etc.; but I could demonstrate, for example, by means of careful histiochemical and physiological investigations, that in arthritis deformans all those changes which can be easily demonstrated in the living by means of Roentgen rays, and which have been characterized by Virchow, Barwell, and Volkmann as the result of puffing, blowing up, disrupturing, grinding, polishing, leading to deformation of the cartilaginous parts of the joints, do not depend on the presence of bacilli but on pathological changes in the process of resorption and secretion of lime. It is the anomalous secretion of lime, principally in the cartilaginous, later also in the synovial tissues of the joints, which leads to necrotic changes in microscopic spots and to a simple inflammatory reaction and small cell proliferation beneath these spots, but not those foci around small vessels, as in the chronic bacillary villous process.

I was enabled to demonstrate this by histiochemical conversion of the surplus of lime into the characteristic crystals of lime oxalate in the cartilage as in the less numerous solid and hard synovial excrescences of arthritis deformans. As a matter of fact they are not necessarily present and not a characteristic feature in arthritis deformans. I had taken many photomicrographs of slices of arthritis deformans as well as of slices of characteristic villous excrescences and of synovials from chronic bacillary villous synovitis, and presented them before the Hufeland Medical Society on July 6, 1899. The paper read on that occasion, with illustrations, appeared in the *Berliner klin. Wochenschrift*, 1900, Nos. 5, 6, and 7, and was entitled "Polyarthritis Chronica Villosa and Arthritis Deformans." I could convince myself later on that neither the hard villi in arthritis

deformans nor those in pure syphilitic cases, nor the rarer ones in other forms of arthritis had dumb-bell shaped bacilli, with one exception, namely, in some cases of chronic villous polyarthritis in joints which at a former period had undergone syphilitic changes. Here I found the characteristic villous excrescences with dumb-bell bacilli, beneath them occasionally deep lacunous defects or flat cicatrizations in the cartilaginous or osseous parts of the joint, and these conditions were seen not only directly at operation on such joints, but even by means of Roentgen rays. In these cases there were also present syphilitic parasites, although, judging from their hyaline condition, syphilis was no longer active in these joints. Antisyphilitic treatment in such cases had no effect. It is possible that preceding syphilis, tertiary as well as hereditary, had given a predisposition to invasion of dumb-bell bacilli into the joints.

I do not know of any special relation of chronic villous polyarthritis to articular rheumatism. Among the great number (230) of my own observations I found only very rarely cases with a history of acute articular rheumatism. In the great majority of the cases the affection began *per se* instantaneously, with villous excrescences which progressed slowly The process took place first in one or in a few joints, as a rule at first in the smaller ones, then gradually in others; sometimes, however, larger joints—the knee for instance—were the first. In my large experience with this form of arthritis I could establish with certainty that it never began with fever and swelling. I do not believe that the well-studied disease, which we are accustomed to call acute articular rheumatism, is ever caused by invasion of dumb-bell bacilli. In my earlier experiments I succeeded occasionally in producing acute serous or seropurulent inflammation of several or nearly all joints in animals, which inflammation resembled acute rheumatism, by injecting cultures of bacteria, especially streptococci, pyogenic, septic (puerperal fever), and others, never, however, by injecting cultures of dumb-bell bacilli. In later publications[1] I distinguished positively between rheumatic arthritis (acute articular rheumatism, chronic rheumatic arthritis), polyarthritis chronica villosa (bacillaris), and arthritis deformans.

Chronic villous polyarthritis bacillaris in men begins usually with the development of villous excrescences. I have often convinced myself of this fact. The growing villous excrescences originate always from distinctly known parts of the synovialis, first described by me as peculiar to every joint, but they grow generally in one direction more massive, and pull, therefore, as a rule the capsule of the joint more in one direction than in other directions. This asymmetric extension of the capsule by the growing villous excrescences is quite a characteristic feature of the chronic villous bacillary polyarthritis. In most cases the villi can easily be felt. The cartilagi-

[1] Zur Behandlung einiger chronischer Gelenkleiden. Mediz. Wochens., 1903, No. 30. Arthritis, Encyclopädie der praktischen Medizin, Wien, 1905.

nous parts of the joints remain unchanged, as can easily be seen in operation and by means of the Roentgen rays. There is the one exception, however, namely, in cases of preceding syphilitic gummatous destruction of the cartilaginous and osseous parts, of which I have spoken above. These destructions can also be differentiated by means of Roentgen rays from the deformations of arthritis deformans. The outside appearance of joints affected by chronic villous bacillary polyarthritic inflammation present, it is true, likewise more or less deformity in many instances, but the type of this deformity is as a rule of quite a different kind from that of the deformity in arthritis deformans. Moreover, there are the different clinical symptoms which characterize the one form and the other, and thus there is no difficulty in distinguishing chronic villous bacillary polyarthritis. Characteristic, for instance, is the lateral roof-tile deviation of the fingers when the metacarpophalangeal joints are affected. This peculiarity is caused by the one-sided protruding growth of the villous excrescences and the very early marked atrophy and palsy of some muscles and nerves.

In the shoulder-joint larger excrescences are rarely noticed. Here I found more often the cicatrizing form, which I call ankylopoietica, while the other form is named hyperplastica. Both forms are, as I could establish by histological and bacteriological examinations, of the same origin and are not seldom found together in different joints of the same patient.

In the elbow-joint the process begins, as I observed, very ofteu in the synovialis under the ligamentum annulare around the head of the radius, and can be diagnosticated here very distinctly by careful palpation. The anterior and posterior cavities of the humerus are likewise the seat of this development, and here they interfere at an early period with articular movements.

In the hand the little joint between the ulna and the radius, as well as the wrist-joint, are affected by the disease, and here it can be easily and early diagnosticated.

The hip-joint is attacked mostly in very severe cases; here it causes fixation in the state of extension.

The knee-joint is very often affected and can be filled with the larger masses of villous excrescences. I am certain many cases described in literature as lipoma arborescens were in reality villous polyarthritis. The asymmetrical clumsy swelling of the joint and the perception of the villi by digital examination facilitate the diagnosis in old cases. But even in recent cases, especially in those near the lateral ligaments and in the circumference of the patella and the ligamentum patellæ, we may notice the first formations of villous excrescences. Those behind the lateral ligaments will early give rise to trouble, pain on digital pressure, and in females sometimes swelling during the time of the menses.

The changes in our affection present quite another picture from,

for instance, those of tuberculous or syphilitic arthritis. Troubles in walking appear at an early period as a rule, but swelling in tuberculosis is usually more diffuse, besides being nearly always connected with a tuberculous focus in some osseous part of the joint, as can be detected by careful Roentgen-ray examination. Roentgen rays may also serve to distinguish between chronic villous polyarthritis and arthritis deformans in cases in which there exists any doubt. Very often, however, the experienced surgeon, simply by means of inspection, palpation, motion, examination for friction sound, etc., will have no difficulty in regard to differential diagnosis.

In the ankle-joint the villous excrescences are mostly found at the outer part of the articulation near the malleolus externus and also near the margin of the cartilaginous surfaces.

In order to arrive at a diagnosis in a case of chronic villous polyarthritis bacillaris we need not necessarily resort to a bacteriological examination, since the symptoms which I have described in my publications, and which I have briefly enumerated here, are very characteristic. I demonstrated, however, in 150 out of my 230 cases the presence of dumb-bell bacilli.

I made cultures from aseptic punctures of unopened joints with a special puncture needle and also from all my operated cases (30). In some cases I excised villous excrescences and parts of the synovialis, placed them between aseptically cemented sterilized glass shells and then in the abdomen of living rabbits, examined them ten to fourteen days later; or placed them in sterilized tubes closed by rubber stoppers in the thermostat, kept them there for a few days at a temperature of 37° to 37.5° C., and then made cultures from these particles on different culture media; or I made cultures after centrifugation of fluid taken under aseptic precautions from a diseased joint. Besides, I made in all cases operated on, and in hundreds of cases treated by injection, dry cover-glass preparations. I am in possession of a large collection of microscopic sections of tissues taken from my operated cases, of cover-glass preparations, and of cultures made after I had experimented with the bacilli on animals, and had many photomicrographs made.

Dr. Fayerweather believes, as stated in his article, that the bacilli which he found in his few cases were not the same as those described by me; but it has to be emphasized that he refers only to my first publication of cultures and experiments on animals from the year 1893, and not to all my later writings. At that time (1893) I was in about the same position as he is now. I had made only a few cultures of bacilli taken from joints affected with our disease and few experiments on animals. I did not, however, give my first observations as conclusive ones, but reserved my opinion until further investigation. As stated already, my observations extend now over 230 cases, which I have studied and described as mentioned above.

In regard to the cultures of dumb-bell bacilli, I wish to reiterate from my last publication that I always stain with Gram. In exceptional cases I found that cultures under Gram treatment would turn a little paler, but they never became discolored. There may arise some misinterpre ation in regard to this point by those who have read only my first communication of 1893, in which I speak of easy staining and decoloring, but this refers essentially to some color ing of the cuts and cover preparations with following simple alcoho washing, not to the staining with Gram, which gives, as stated, no difficulty.

The dumb-bell bacilli, according to latest measurements which I took last summer[1]—and I had a large collection of my own cultures of microscopic preparations, to serve for my purpose—showed the following proportions: length 1 to 2 to 4 μ, width 0.25 to 0.75 μ.

After repeated inspection of many microscopic preparations of slices, cultures, dry cover-glass specimens, taken from patients as well as preparations taken from joints, blood-cultures from animals, I am certain that the name I have given to the bacillus causing polyarthritis chronica villosa in the joints, although not conspicuously adaptable in every specimen, characterizes without question, in the greater majority, very well the form of the bacilli, and, therefore, I wish to suggest to retain this name "dumb-bell shaped bacilli" exclusively for the bacilli of polyarthritis chronica villosa.

In some exceptional cases they are very short and clumsy with only a light compression in the middle, so that they resemble somewhat gonococci, but they become stained with Gram, while the gonococci will be decolorized by Gram; besides the thick, short forms develop the longer dumb-bell shape as soon as they grow on a suitable culture soil. The same applies to the other varieties of the form which seem to be influenced by the different conditions of nutrition, as well in tissues of men and animals as in the culture soil.

In other exceptional cases they resemble diplococci, but as a rule the dumb-bell shape is very striking, with roundish poles and a middle part. The middle part may be short or unusually broad; there are found also sometimes specimens in which the lateral parts are more rod-like, etc. Sometimes they lay singly, sometimes they are arranged regularly, two by two, like diplobacilli, etc. Since I found the different forms and relations not only in the tissues of the same case, but very often in different cultures and in different soils, and found that the different forms originate from bacilli of one and the same first or typical form, and as this fact became confirmed very often in my cases, as for instance again in a case of disease of the knee joint in a man of fifty years, operated on a few months ago, I cannot think that these modifications of form cor-

[1] Berlin. klin. Wochenschr., 1905, No. 40.

respond with different kinds of bacilli, but I am convinced that they all are the same original bacilli which I have named dumb-bell bacilli of polyarthritis chronica villosa.

Comparing the culture table of Dr. Fayerweather given in his article with many cultures, I think that his Bacillus 1 and Bacillus 3 are identical with my dumb-bell bacillus; form, measure, staining by Gram are the same; in addition many of the culture properties are almost the same as far as I can judge. His Bacilli 3 and 4, decolorized by Gram, must be excluded, and the cases from which they were taken are not cases of polyarthritis chronica villosa.

In excluding those cases we exclude the supposed etiological connection of polyarthritis chronica villosa with acute articular rheumatism, to which latter class belongs Fayerweather's fourth case; it has nothing to do with the disease which I call polyarthritis chronica villosa.

It is true, however, as pointed out before, that joints which at sometime previously have been the seat of rheumatism may likewise become the seat of a chronic villous bacillary process, exactly as it may well happen that at some remote period a gonorrhœic or other form of arthritis existed in these joints; but such occurrences are rare, and when they happen, we may find in the joint beneath the dumb-bell bacilli small accumulations of gonococci or other pyogenic bacteria. I have had some such cases under observation. Some months ago I operated on the knee joint of a patient, and in this case I at first believed that there existed a complication: dumb-bell bacilli and gonococci together, when I recollected that nine years ago I had operated on the other knee joint of this patient—with best success as to mobility—and at that time had found numerous rather long dumb-bell shaped bacilli. Staining with Gram and cultures, which I made after the last operation, proved the error: there were no gonococci, but only dumb-bell bacilli.

Summing up, I wish to say that I am convinced the disease which I described as polyarthritis chronica villosa is caused only by the bacillus which I have called dumb-bell shaped, and not by any other kind or form, and that this disease has no near etiological relations with acute rheumatic arthritis. It is to be hoped that my statements given in this paper will induce others to make further investigation. I shall be especially gratified if American colleagues will follow Dr. Fayerweather, to whom I am thankful for his interest in my labors, in studying the matter on a larger scale.

PEPTIC ULCER OF THE ŒSOPHAGUS.

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By simple or peptic ulcer of the œsophagus is understood an ulcer situated in the lower part of the œsophagus and bearing a close resemblance to the simple ulcer of the stomach. It is a condition which has received little attention in this country, although not excessively rare, and it has, therefore, seemed worth while to report the following three cases, and to give a general discussion of the disease.

For the better comprehension of the subject it will be advisable, first, to consider briefly ulcerations due to other causes, which must be ruled out before the peptic nature of the lesion can be admitted. Of these, twelve forms may be distinguished: (1) carcinomatous, (2) due to the action of corrosive substances, (3) due to foreign bodies, (4) occurring in the course of acute infectious diseases, (5) decubitus, (6) due to aneurysm, (7) catarrhal, (8) due to traction diverticula, (9) tuberculous, (10) syphilitic, (11) varicose, (12) due to thrush. The first three forms are sufficiently well known to be dismissed without further consideration.

Ulcers of the œsophagus have been reported as postmortem findings in the following acute infectious diseases: diphtheria, scarlatina, variola, typhoid fever, and pneumonia. They are due to acute inflammation, and bacteria are found present.

In diphtheria, Councilman, Mallory, and Pearce[1] found membrane in the œsophagus in twelve out of 220 autopsies, or 5 per cent. The lesions consisted of longitudinal erosions with sharply cut edges, and covered with adherent fibrinous membrane. Leube[2] states that stenosis may follow.

In scarlatina the process is a diffuse inflammation with ulceration, invading the œsophagus by extension from the pharynx; it may be followed by stenosis. The ulcers in variola arise from the breaking down of œsophageal pocks. Louis and others have called attention to ulcers in the œsophagus, occurring in typhoid fever, usually in the upper part, and accompanied by ulceration of the pharynx; the specific bacilli have not yet been demonstrated in them. They, too, may be followed by stenosis. Of lesions occurring in croupous pneumonia I have found but two instances: (1) a case of Kraus,[3] in an elderly female; numerous hemorrhagic infiltrations in the lower half of œsophagus, hemorrhagic erosions, and

[1] A Study of the Bacteriology and Pathology of 220 Fatal Cases of Diphtheria, Boston, 1901.
[2] Specielle Diagnose der inneren Krankheiten, Band i. S. 262.
[3] Die Erkrankungen der Speiserohre, p. 193.

small ulcers near the pylorus; (2) a hitherto unpublished case from the Boston City Hospital: a man, aged fifty-four years, croupous pneumonia of the right upper and middle lobes; at the middle of the œsophagus on the posterior wall an irregular superficial ulcer, 2.5 x 6 cm., covered with diphtheritic membrane; microscopic examination showed a fibrinous membrane, with no Klebs-Loeffler bacilli. Cultures from the heart, lung, liver, and kidneys all showed the presence of pneumococci.

Decubitus of the œsophagus occurs on the anterior or posterior wall, or both, corresponding in size and situation to the posterior part of the cricoid cartilage, to the pressure of which it is due. It is seen after death from wasting diseases, especially typhoid fever and tuberculosis.

The ulceration which sometimes accompanies aneurysm of the descending aorta is probably likewise due to pressure; necrosis of the mucous membrane first takes place, followed by ulceration and perforation.[1]

Catarrhal ulcers are rare; they are small and shallow, involving only the mucous membrane, with irregular edges; they are accompanied by catarrhal œsophagitis. The so-called follicular ulcers occupy the site of the mucous glands, and are small and cup-shaped.

Ulcers due to traction diverticula may show a superficial resemblance to peptic ulcers, but their situation, usually at the bifurcation of the trachea, and the presence of shrunken adherent lymph glands, reveal their true character.

Tuberculous ulcers of the œsophagus are very rare; they are usually shallow, with necrotic, purulent bases, resembling tuberculous ulcers of the mouth and pharynx. Tubercles may be found in the walls of the ulcer, and there is always tuberculosis of other organs.

Ulceration occasionally takes place in the mucous membrane over an œsophageal varix; the wall of the vein is soon perforated, and death takes place by hemorrhage before the ulcer attains a considerable size.

Ulceration from thrush is rare and occurs almost exclusively in infants.

From this brief account of the various ulcers to be met with in the œsophagus, I now pass to the consideration of the subject of this paper, peptic ulcer.

HISTORY. Ulcer of the œsophagus, resembling peptic ulcer of the stomach, was first described by Albers in 1839. From that time on, occasional cases were reported by Flower, Reeves, and others, and the existence of such ulcers was admitted by so great an authority as Rokitansky. Zenker, writing in 1878, and Birch-Hirschfeld, claimed that the ulcer in all these cases was

[1] Fr. Kraus. Die Erkrankungen der Speiserohre, p. 178.

due to carcinoma, perforated traction diverticula, and other causes, and they denied the occurrence of peptic ulcer in the œsophagus. In the following year, however, Quincke published three cases in which the peptic nature of the ulcers seemed clearly proved, and a careful microscopic examination left no loop-hole for criticism. It is owing to him that the disease became established as a definite entity. Since then cases have been reported by a number of observers, of whom Chiari, Debove, Ortmann, and Kraus have added most to our knowledge of the subject. Excluding all cases before those of Quincke on the ground of uncertainty of diagnosis, there have been reported up to the present, forty-one cases of peptic ulcer of the œsophagus; of these, eight were without autopsy, but from the clinical picture the diagnosis seems reasonably certain. I have been able to collect three other cases, hitherto unpublished, one of which came under my personal observation; this makes a total of forty-four cases, on the analysis of which the following statements are based.

ETIOLOGY. The disease in question, though rare, is probably not so infrequent as might be supposed from the small number of cases reported. A study of the records of the Massachusetts General, Boston City, and Long Island Hospitals showed that peptic ulcers of the œsophagus were noted in six cases out of 4496 autopsies, *i. e.*, 0.13 per cent.

AGE. Ulcer of the œsophagus occurs from infancy to old age; the youngest reported patient being three days old, the oldest sixty-six years. It is met with most frequently in middle age, as the following table shows:

Age.	*Cases.*
0 to 9	5
10 to 19	2
20 to 29	5
30 to 39	5
40 to 49	11
50 to 59	8
60 to 69	4
Total	40

In three cases it has been found as the source of the bleeding in hemorrhagic disease of the newborn.

SEX. Of forty cases in which the sex was specified, twenty-eight were males and twelve females; out of twelve cases with complicating ulcers in the stomach or duodenum, there were eleven males and but one female. A similar preponderance in favor of the male sex is found in duodenal ulcer, whereas ulcer of the stomach, as is well known, occurs more frequently among women. This may be due to the greater frequency of alcoholism among men, as Boas has suggested for duodenal ulcer.

PREVIOUS DISEASE. In order that peptic ulcer should be formed, it is evidently necessary that the cardia should be insufficient, allowing regurgitation of the gastric juice into the œsophagus. An important part is played in the etiology, therefore, by diseases accompanied by frequent vomiting, such as peritonitis, nephritis, chronic gastritis, and especially ulcer of the stomach or duodenum. In the disease last mentioned, besides the vomiting, two factors are of importance: (1) ulcer of the cardia with organic insufficiency; (2) stenosis at the pylorus, with dilatation of the stomach, which may involve the cardiac orifice, with consequent relative insufficiency. The importance of the second factor is shown by the presence of stenosis of the pylorus or duodenum in eight of the cases with autopsy, or 23 per cent.

In nephritis, besides the frequent vomiting, the deleterious action of the uræmic poison on the tissues is probably effective. Disease of the kidneys was found in four cases; it was probably present oftener, as in many instances the condition of the kidneys is not mentioned.

That peptic ulcer may result from mercurial poisoning seems probable from the following case occurring at the Massachusetts General Hospital (service of Dr. R. H. Fitz): Minnie P., female, aged thirty-seven years, entered the hospital November 26, 1901, with general œdema and advanced failure of compensation. There was a history of frequent vomiting lately. She received, for purposes of diuresis, 63 grains of calomel in seven days, combined with opium and digitalis. The stools became frequent and bloody, and there was hemorrhage from the gums also. Death took place December 5th. At the autopsy were found a dilated heart, with double lesions of the mitral and aortic valves; chronic passive hyperæmia of the kidneys, lungs, liver, and spleen, and severe diphtheritic colitis; in the lower part of the œsophagus were four or five shallow ulcers involving the mucous membrane only, with reddish, finely granular bases, and irregular outlines, the largest 12 mm. in diameter; the surrounding mucous membrane was healthy; the stomach was normal. No microscopic examination of the ulcers was made. The lesions in the intestine corresponded with those found in acute mercurial poisoning.

In this case it must be admitted that it is possible the ulcers were due to the action of mercury, either alone or combined with passive hyperæmia. In view, however, of the situation in the lower part of the œsophagus, and of the opportunity offered for the action of the gastric juice by the frequent vomiting, it seems reasonable to assume that the mercury acted merely as a predisposing cause, and that the ulcers were peptic.

Chlorosis, which has been supposed to favor the development of ulcer in the stomach, probably plays no part in the production of œsophageal ulcer, for it was not present in any of the cases.

OTHER FACTORS. The abuse of alcohol deserves mention among the predisposing causes, occurring with considerable frequency. Alcohol probably acts in two ways: first, by irritation of the œsophagus, and second, by the production of gastritis, with vomiting and insufficiency of the cardia.

Various lesions of the heart and vessels have been found present, and may be of some importance in etiology, through disturbance of nutrition in the œsophagus. Among them arteriosclerosis, aortic aneurysm, hypoplasia of the aorta, and myocardial degeneration may be mentioned. In a case of Carstens with amyloid disease, it is uncertain whether the diseased condition of the vessels or the accompanying nephritis was effective.

The possibility of a traumatic origin must be considered next. Ortmann has reported cases in which the first symptom came on after swallowing food of an irritating nature, *e. g.*, sour wine, and in which he assumed that spasm of the œsophagus took place, producing a tear in the wall, which became a starting point for the ulcer. It is possible, however, that the ulcer already existed in a latent form, and the question cannot be considered settled.

The relation of the acidity of the gastric juice to ulcer is an interesting one, but unfortunately the point was noted in only seven instances. Of these, four were complicated with ulcer of the stomach (or duodenum); free HCl was "present" or increased in three, diminished in one case. In the three cases in which the ulcer was in the œsophagus alone, HCl was "present" in two cases, increased in one. The figures are too few for any deductions, but one would expect hyperacidity to be the rule, as in gastric ulcer.

Large abdominal tumors were present in three cases, in one of which there was also cancerous peritonitis. Quincke expressed the opinion that here, by the pushing up of the diaphragm, a kinking of the œsophagus was produced, which in turn caused circulatory disturbances favorable to ulcer formation. Acute and chronic peritonitis, each noted in two instances, might be efficacious in two ways, by causing vomiting, and by pressure on the diaphragm (meteorism).

Fischer[1] has reported ulceration of the œsophagus after extensive burns, analogous to ulcer of the duodenum under like circumstances. Probably thrombosis or embolism is the primary event here, due to disintegration of the red cells of the blood, or possibly to septic processes.

It remains to discuss the possibility of a nervous origin for the ulcer. Guitéras has reported the following case, which he considered to be peptic ulcer due to hysterical ischæmia and merycism: A woman, aged forty-four years; had nervous prostration nine years

[1] Quoted by Huwald, p. 24. (See bibliography.)

before; two years later, difficulty with swallowing, especially with liquids; globus hystericus. Eighteen months before entrance to the hospital a similar attack, but more severe, was cured temporarily by the passage of bougies. Return of symptoms, with complete inability to swallow; emaciation and death. At autopsy the œsophagus, from a point four and one-half inches below the cricoid to the cardia, was riddled with ulcers, pin-head to pea-sized, for the most part superficial; opposite the bifurcation of the trachea were two larger ulcers, which had perforated into the mediastinum; numerous pigmented scars, apparently of healed ulcers, were also present.

The earlier symptoms in this case point clearly to nervous spasm of the œsophagus, and in this condition it is known that secondary dilatation may take place, with stagnation of food in the œsophagus. In a few of these cases[1] numerous thickly set ulcers have been found, very similar to those described by Guitéras. In view of these facts, the peptic character of the ulcers in his case seems very doubtful, and I have, therefore, not included it in this series.

There are no other cases in the literature which point to a nervous origin of œsophageal ulcer, and from what we know of gastric ulcer such an origin does not seem probable.

Pathology. Simple ulcer of the œsophagus resembles very closely, both in gross and microscopic appearances, simple ulcer of the stomach. It is situated, as a rule, in the lowest part, close to the cardia, as one would expect from the peptic origin. Usually it stops short at the cardia; in six cases, however, or 17 per cent. of the thirty-six cases which came to autopsy, it involved the adjacent part of the stomach also, and the appearance of the ulcer pointed to a primary seat in the cardia, with invasion of the œsophagus by direct extension. It may reach as high as the bifurcation of the trachea, but single ulcers situated at this level (as in Part's case[2]) are to be viewed with suspicion, as it is not likely that the gastric juice would exert its action at such a distance from the stomach. Of the seven cases in which definite statements are made as to the situation, the ulcer was in the anterior wall twice, in the posterior wall three times, on the left side twice, and three times on the right; the right posterolateral wall seems, therefore, to be the seat of predilection. The size varies greatly, from that of a pea or smaller to ulcers involving the entire surface from the cardia to the bifurcation. In most of the cases (81 per cent.) but a single ulcer is present; in others they are very numerous. It is probable that some of the large, irregular ulcers arise by confluence. The smaller ulcers are mostly round or oval, the larger are irregular, often girdling. If very recent, the loss of substance is slight, involving only the mucous membrane, usually irregular in outline,

[1] See A. Neumann. Centralbl. f. d. Grenzgebiete d. Med. u. Chir., iii., 253; and A. Schmidt. Münch. med. Woch., 1899, p. 304.

[2] Lancet, 1857, p. 167.

with clear cut edges and red, granular base. Older ulcers usually lay bare the muscular coat, and may show the typical punched-out appearance and funnel-shaped base of the gastric ulcer; if of long standing, the base is smooth and the edges may be undermined. The surrounding mucous membrane is healthy as a rule; there may be dilatation of the lower œsophagus, even when no stenosis is present.

The ulcer, like its namesake in the stomach, has a strong tendency to perforation, which took place in six cases: twice into the right pleural cavity, once into both, with double pneumothorax, and once each into the aorta, pericardium, and lesser omental cavity. In Janeway's case, without actual perforation, there was inflammation of the periœsophageal tissue, pericarditis, and pleurisy.

Microscopically, there are found the usual appearances of chronic inflammatory tissue, with the absence, of course, of evidence of cancer, tuberculosis, etc. In two cases, thrombosed arteries were found in the base. In Fraenkel's case, Stoerk found at the edge of the ulcer glands identical with those found in the stomach; Schaffer[1] and others have noted the presence of such glands in the normal œsophagus; there were similar findings in my first case. Kraus, however, sought them in vain in three instances.

Healing takes place frequently, with the production of a scar. Scars were found, either alone or in conjunction with fresh ulcers, in nine cases, or 25 per cent. They may be puckered and radiating, as in the stomach. If small, they do no harm; the larger ones by contraction produce stenosis. In one case (Ortmann) a carcinoma of the œsophagus was found developing from the scar of an old peptic ulcer; I have seen the specimen from a similar case, at the Pathological Institute in Vienna.

The cases of peptic ulcer may be divided into three groups: (1) those in which the œsophagus alone is involved; (2) those showing extension from the cardia; and (3) those with ulcers in other parts of the stomach or in the duodenum. The first group is much the largest, with twenty-two cases, or 61 per cent. of the cases with autopsy. The second comprises six cases (17 per cent.) and the third twelve cases (33 per cent.). The last two groups cannot be sharply separated, because in several instances both the cardia and other regions of the stomach were involved. The distribution of the ulcers in the third group was as follows: anterior wall, one case; posterior wall, one case; pylorus, five cases; duodenum, five cases. Stenosis of the pylorus and of the duodenum, with dilatation of the stomach, were each present four times. In the case of Kraus, besides stenosis of the duodenum, there was an hour-glass stomach. In three instances death was due to the perforation of a gastric ulcer.

[1] Beiträge zur Histologie menschlichen Organe, Sitzungsberichte der Wiener Akademie, October, 1897, Band. cvi., 3 Abth.

Hemorrhagic infiltration of the œsophagus, with numerous erosions in the stomach, was reported by Kraus in a case of pneumonia. From the resemblance of the lesions to those seen in the stomach in certain cases of septicæmia, an infectious origin seems probable, and I have, therefore, classified it among the ulcers of acute infectious diseases.

Ulceration of the œsophagus in hemorrhagic disease of the newborn demands a separate consideration. There are three such cases in the literature. The first (Henoch) showed a deep ring-shaped ulcer, 2 cm. long, just above the cardia, with gray-white, infiltrated base; the throat was normal (no diphtheria). In Spiegelberg's case there was a pea-sized area of hemorrhagic infiltration at the junction of the cardia and the œsophagus, with superficial necrosis; microscopic examination showed no lesion of the vessels; blood-cultures during life were sterile. In the third case (Meyer) the lesion consisted of an ulcer immediately above the cardia, with an elongated thrombus measuring 6 x 7 x 12 mm., tightly adherent. Microscopic examination showed inflammatory infiltration of the base and edges of the ulcer, with streptococci and long bacilli in these tissues, and also in the circular muscular coat; sections of the liver, spleen, and kidneys showed no bacteria; no cultures were made. The stomach and intestines were normal in all.

The presence of bacteria in the tissues in the last case, and of hemorrhagic infiltration in the second, are strongly suggestive of a bacterial origin, a view that is often taken nowadays of hemorrhagic disease of the newborn in general. The lesions just described resemble those found in the stomach and duodenum in a few other cases of this disease. The sequence would appear to be hemorrhagic infiltration (due to capillary embolism), necrosis, then digestion by the action of the gastric juice, with ulceration.

Lesions in Other Organs. Of these the most interesting are the abdominal tumors, which were present as the primary disease in three cases; curiously enough, they all arose from the ovary Whether this is anything more than a coincidence must be left to the future to decide. The nature of the growth was as follows: carcinoma of the ovary with cancerous peritonitis (Quincke), enormous cyst (Quincke), fibroma the size of a man's head (Sabel).

Chronic interstitial nephritis was noted in four cases, in one of these combined with amyloidosis of the liver and spleen. Tuberculous peritonitis and acute general peritonitis were each present twice; the latter was due to perforation of a gastric ulcer and of the gall-bladder respectively. Cirrhosis of the liver and phthisis were each present in two cases. In the case of Dasse, there was an aneurysm of the aorta, the size of a hen's egg, adherent to the œsophagus. The aneurysm was situated at the fourth dorsal vertebra, the ulcer 4 cm. above the cardia; the distance between the two renders any direct causal relationship doubtful.

PATHOLOGICAL DIAGNOSIS. This may be summed up as follows: an ulcer in the œsophagus is to be regarded as peptic when it presents the appearances already described, is situated in the lower part of the œsophagus, and none of the other causes of ulceration are present. The finding of similar ulcers in the stomach or duodenum strengthens the diagnosis.

PATHOGENESIS. As already mentioned, the first requisite for the formation of the peptic ulcer of the œsophagus is an insufficiency of the cardia. This may be organic in the cases in which the ulceration is at the cardia; in the rest it is functional. Normally the cardia is closed, owing to the tonic contraction of the circular fibres. Relaxation takes place through inhibitory impulses from the vagus fibres, and occurs with the act of swallowing, and with pyrosis, belching, and vomiting. Another source of insufficiency is a decrease in tone of the cardiac sphincter, similar to that which occasionally takes place at the pylorus. In this connection, it should be mentioned that a rhythmical relaxation of the cardia has been observed in some animals during digestion, with regurgitation of food into the œsophagus.

Evidently insufficiency must occur frequently without producing ulcer; for the formation of an ulcer something else must be added. It is generally admitted for gastric ulcer, that the first step is a necrosis of the mucous membrane, which then becomes digested away by the action of the gastric juice, with resulting ulcer formation. But why the necrosis takes place has never been satisfactorily explained. The prevailing theory is that it is due to circulatory disturbances of one sort or another. Infectious thrombosis has been assumed as a cause, and probably holds good in some cases of hemorrhagic erosion, but has not been shown to occur in peptic ulcer. Thrombosis of an artery in the base of the ulcer has been demonstrated in two cases (Zahn and first case of Tileston), but was probably secondary in the first, and certainly in the second, in which there was also erosion of the arterial wall. Quincke's theory of kinking of the œsophagus, owing to upward pressure on the diaphragm, would account for only a limited number of cases. That hyperacidity of the gastric juice plays a part in preventing healing of the ulcer seems probable, but the data on this point are insufficient for definite conclusions. In short, the real cause of peptic ulcer of the œsophagus, as is the case with gastric ulcer, remains hidden.

Before passing to the description of the clinical picture, I have to report three new cases, which possess several interesting features.

CASE I.—From the service of Dr. J. J. Minot, Long Island Hospital, Boston.

Catherine C., aged fifty-eight years, widow, was admitted on March 23, 1905, in a moribund condition, and died one hour afterward. No physical examination was made. The history obtained

from a friend later was unsatisfactory. Fifteen years ago amputation of the left leg was performed; cause not ascertained. Eight years ago she was in a hospital with "heart trouble." Cough and dyspnœa for several days previous to admission; no symptoms referable to the œsophagus.

Autopsy: Ninety-one hours postmortem. Dr. G. B. Magrath.

Anatomical Diagnosis: Chronic adhesive pleuritis; hydropneumothorax; atelectasis; acute vegetative endocarditis (mitral); fatty infiltration of the myocardium; ulcer of the œsophagus with perforation into the pleural cavity; chronic perisplenitis; fatty metamorphosis of the liver; chronic nephritis; hemorrhagic infarction of the kidneys; hemorrhagic pachymeningitis; general arteriosclerosis (slight).

Body that of a woman, aged fifty-eight years; length 142 cm.; well-developed and nourished. On the trunk and inner aspect of the thighs a brown, macular, and somewhat diffuse pigmentation, emphasized over the abdomen and at the axillæ; the skin of the right lower leg and ankle shows faint, whitish, irregular scars.

Subcutaneous fat 3 cm. in thickness; muscles fairly well developed, rather fatty. Chest wall prominent and convex; height of diaphragm, sixth rib on right side, fifth rib on left. Puncture of the wall of the right chest is followed by the escape of numerous bubbles of air or other gas.

Pleural Cavities: Left: interrupted by rather numerous dense fibrous bands, and contains 500 c.c. of clear serous fluid; right: contains 1300 c.c. of yellowish, somewhat turbid fluid, with strings of fibrin; a few fibrous adhesions at the apex and base; the inrne wall, just above the diaphragm, presents an elliptical opening, 3 x 6 cm., apparently communicating with the œsophagus, and with edges slightly rounded; the adjoining pleural surface a little roughened.

Œsophagus: On the right lateral and posterior walls, at a level 2 cm. above the opening into the stomach, an irregularly oval ulcer, its vertical axis 3.5 cm., the transverse 2 cm.; the edges are rounded, somewhat inverted, and perfectly smooth; the floor is somewhat uneven, gray, mottled with yellow, and fairly firm; the depth is about 1 cm.; the edges are extensively undermined, and the left border a good deal indurated; in the deepest part of the ulcer is the opening into the pleural cavity, already described. The neighboring lymph nodes and those along the lesser curvature of the stomach are of the size of beans, upon section, extensively pigmented but otherwise negative.

Pericardial Cavity: Normal.

Heart: Weight, 305 grams; epicardial fat fairly abundant; on the epicardium of the right ventricle fairly numerous punctate hemorrhages; myocardium pale brown-red, and rather limp; that of the right ventricle shows some invasion of the epicardial fat. Wall of left ventricle 1.3 cm., of right 0.3 cm. in thickness. Mitral

valve 10, aortic 7, pulmonary 7, tricuspid 11 cm. in circumference. Depth of left ventricle 9 cm. Cavities of both ventricles a little dilated. Both curtains of the mitral valve show nodular vegetations along the line of apposition, grayish, translucent, and granular, and about 0.4 cm. in elevation; on the anterior curtain there is also a "cauliflower" excrescence. The right posterior cusp of the aortic valve shows a calcareous nodule at its base. Pulmonary and tricuspid valves normal. Coronary arteries fairly smooth.

Lungs: Left: moderately crepitant throughout; slight scarring at the apex; the lobes interadherent; upon section, gray-red, under pressure yielding a little frothy fluid; bronchial lymph nodes black. Right: of diminished volume; lies back in the pleural cavity close against the inner wall; slaty gray; the pleural surface for the most part smooth, with here and there an attached fibrous tag and shred of fibrin; the upper and middle lobes interadherent, the apex without scars; the upper lobe somewhat crepitant and downy; the lower lobe flaccid and non-crepitant; careful inspection reveals no opening upon the pleural surface, or in the walls of the primary bronchi; upon section, similar to the left lung.

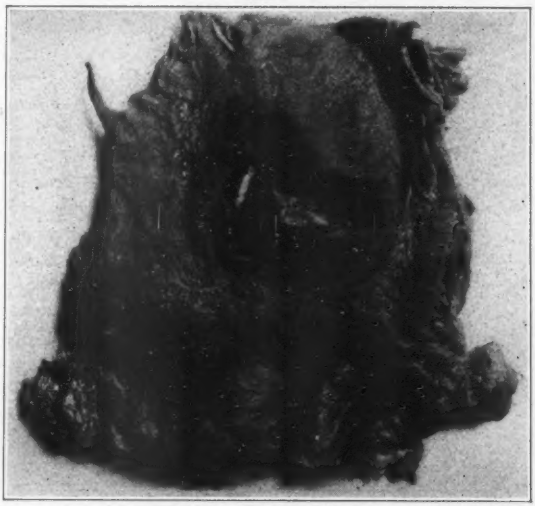
Abdomen: Peritoneal cavity interrupted by fibrous adhesions, uniting the spleen and the surrounding structures, and by others in the region of the foramen of Winslow. Spleen: weight 120 grams; bound down by adhesions, extensively fragmented upon removal; garnet red; markings indistinct; pulp seemingly increased. Stomach normal. Intestines: the ileum in its upper portion shows moderate injection of the veins and is of a general pale brick-red color; upon section, containing thin, semifluid material of the same color; colon empty. Vermiform appendix normal. Liver: weight 1200 grams; extensively dislocated downward; the surface in general smooth; general color pale brown; upon section, lobular markings distinct; the centres brown and a little depressed, the borders pale brown; consistence friable. Kidneys: weight of both 210 grams; capsule somewhat adherent to a surface marked by numerous shallow, in some instances, fairly deep scars, often linear, and giving to the organ a lobulated appearance; general color grayish-red; left: upon its posterior border, about midway between the poles, presents a cyst, 4 cm. in diameter; right: upon section, shows within the cortex here and there small dark-red splotches, 2 to 3 mm. across; cortex 0.5 cm. in average thickness; reddish-brown; glomeruli visible; consistence increased. Genitalia: uterus negative; appendages show senile atrophy. Aorta shows an inner surface mainly smooth, with a few slightly elevated non-calcified patches of yellowish thickening in the abdominal segment and in the arch. Gall-bladder, pancreas, adrenal glands, and bladder not remarkable.

Cranium: Sinuses normal; the dura of the right occipitoparietal region upon its inner aspect presents rather numerous, irregular,

slightly elevated, dark-red areas, for the most part 1 cm. across, to some extent, confluent; the overlying inner surface smooth. Brain: vessels of the base for the most part normal; the internal carotid arteries at the turn showing a little thickening; upon section, negative; the subdural space contains a little more than a normal amount of fluid. Spinal cord not examined.

Histological Examination. Œsophagus, ulcer: section of a segment through the left side of the ulcer, including the floor to its centre: at the free edge of the ulcer there are villi devoid of epithelium; here the submucosa contains a rather large number of widely dispersed plasma and lymphoid cells; the villi of the glands at the turn of the edge are lost in a zone of necrosis, about 0.5 mm.

FIG. 1



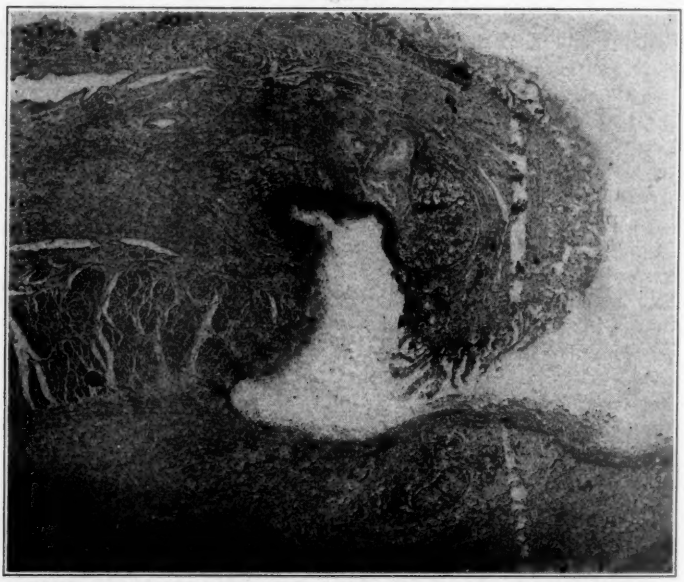
Gross appearances of the ulcer of the œsophagus (⅘ natural size), showing the perforation.

in breadth, which extends along the entire surface of the ulcer; the loss of substance involves the muscle coats and the connective tissue beneath them; outside of the zone of necrosis the tissues contain fairly numerous lymphoid and plasma cells, with occasional leukocytes and young connective-tissue cells, and in places newly formed bloodvessels. At several points small arteries lead into the surface of the ulcer, and one of them presents erosion of its wall upon the side toward the ulcer and is partially occluded by a thrombus which is continuous with the floor of the ulcer. Beneath the surface of the deepest part of the ulcer is fat tissue which has been largely replaced by a rather loose-meshed connective tissue, containing large, sometimes stellate cells in a fibrillar stroma; here and there,

particularly around the bloodvessels, are groups of lymphoid and plasma cells. Near the edge of the ulcer, in the submucosa, is a large group of glands with columnar epithelium, resembling mucous glands in structure.

A section of the œsophagus a short distance above the level of the ulcer shows the following appearances: muscular coats normal; epithelial layer absent (postmortem change); the mucous surface is represented by villous-like stalks of connective tissue. In the submucosa are cross-sections of several ducts.

FIG. 2



Microscopic section of the ulcer of the œsophagus, showing the overhanging edge.

Kidney: There are many small, irregular areas of slight connective tissue-increase, and numerous masses of connective tissue extending inward from the capsule, like trabeculæ. In these regions there are many atrophied tubules and sclerosed glomeruli. In some there is abundant infiltration, with lymphoid and plasma cells. There is slight endarteritis and moderate perivascular increase of connective tissue. Many Henle and collecting tubules are filled with hyaline material. Histological diagnosis: chronic interstitial nephritis.

The accompanying illustrations (Figs. 1 and 2) give a good idea of the gross and microscopic appearances of the ulcer. The photomicrograph is by L. S. Brown, of the Clinico-Pathological Laboratory of the Massachusetts General Hospital.

In this case the typical appearance of the ulcer and the situation make the diagnosis of peptic ulcer certain. That the perforation took place during life is shown by the existence of acute inflammation of the pleura of the corresponding side. Interesting features are the apparent latency up to the time of perforation, the presence of chronic nephritis, and the close resemblance of the mucous membrane about the ulcer to that normally found in the stomach.

CASE II.—George R., a cabman, aged fifty-nine years, was sent to the Massachusetts General Hospital (service of Dr. W. L. Richardson), on June 15, 1902, by Dr. Roscoe E. Brown, to whom I am indebted for the history. The patient had been failing for some months, suffering from retention of urine due to stricture of the urethra. His digestion was upset, and for a few weeks previous to entrance to the hospital he had difficulty in swallowing solid food; during the last two days he could take nothing but liquids. There was a good deal of pain and vomiting. The patient on entrance was semicomatose, delirious, and apparently in great pain. From time to time he vomited a thin fluid tinged with blood. Death took place in coma fifteen hours afterward.

Autopsy, twenty-two and one-half hours postmortem. Dr. J. H. Wright.

Anatomical Diagnosis: Chronic interstitial nephritis; extensive ulceration of œsophagus; chronic interstitial orchitis; focal tuberculosis of the left kidney; slight arteriosclerosis of the aorta.

The lower end of the œsophagus for a distance of 11 cm. is denuded of mucous membrane, except for a few small islands, and of a dirty brown-yellow color. The ulceration is very shallow, not involving the muscularis. The bordering mucous membrane has smooth edges, and is not discolored. At the upper margin the loss of substance is continued upward in the form of two irregular streaks; the longest is 5 cm. No microscopic examination was made. The mucous membrane of the stomach of a dirty slate color.

Kidneys: left, 36 grams; right, 97 grams. Capsule adherent; cortex very narrow; normal markings absent. In the left, several sharply defined, opaque, firm, yellowish masses, the largest 3 mm. in diameter.

In this case the ulceration is more acute in character than in the preceding, and probably extended rapidly during the last few days, when the patient was in the uræmic state. In spite of the lack of microscopic examination there can be no doubt of the diagnosis.

CASE III.—Martha H., aged twenty-seven years, widow. Admitted to the Massachusetts General Hospital, April 30, 1898 (service of Dr. F. C. Shattuck). One year before, stomach trouble with anæmia. For two weeks, gastric pain, vomiting, and prostration. This morning taken suddenly with severe abdominal pain. An immediate operation (Dr. F. G. Balch) revealed general

peritonitis, but no perforation could be found. Death took place the next day.

Autopsy, three and one-half hours postmortem. Dr. J. H. Wright.

Anatomical Diagnosis: Ulcus ventriculi with perforation; general acute fibrinopurulent peritonitis; slight ulceration in the œsophagus; obsolete tuberculosis of mesenteric glands; œdema of pia; laparotomy wound.

Peritoneal cavity full of yellow, cloudy fluid containing flocculi. Stomach adherent to left lobe of liver. Ulcer in anterior wall of stomach, midway between pylorus and cardia, presenting irregular perforation 1 cm. in diameter, with smooth edges. This opening leads to an abscess cavity the size of a bean, between the stomach and liver, surrounded by chronic inflammatory tissue. No evidence of cancer about the ulcer.

Œsophagus: In the œsophagus, several losses of substance; ulcers shallow, with ill-defined edges and rather dark-red, granular bases. Microscopic examination of œsophagus: in places the epithelium absent, exposing the submucosa or membrana propria, in which there is a marked infiltration with plasma cells.

In this case, therefore, we see a chronic ulcer of the stomach with perforation, resulting in localized, and later general peritonitis. The œsophageal ulcers are of very recent date, judging from their superficial character and fresh granulations. They probably occurred some time after the first perforation of the ulcer of the stomach. The infiltration with plasma cells shows that the process took place during life.

I now return to the general discussion of the disease and pass to the clinical aspect.

Symptoms. In a large proportion of the cases the ulcer has not been suspected during life, being either entirely latent, or giving rise to no symptoms sufficiently characteristic for a diagnosis. In another group, it has remained latent up to the time of perforation. The symptoms vary in different stages of the disease according as the ulcer is open or healed. The most prominent manifestations of the stage of ulceration are five, namely, pain, dysphagia, vomiting, hæmatemesis, and perforation. Owing to their importance it will be best to consider each in detail. The cases in the newborn are not included in this discussion. The only symptoms they present are hæmatemesis and melæna.

Pain: This is the most constant symptom. Out of thirty-four cases in which the history is given it was present in 82 per cent. The pain was of such a character as to suggest an origin in the œsophagus in 60 per cent. of those cases in which it was accurately described. The characteristic location is at the xiphoid cartilage, or beneath the sternum, radiating to the back between the shoulder-blades. In some cases it was referred by the patient directly to

the lower end of the œsophagus, in others, to the front of the chest. In a few instances the pain was epigastric, although the ulcer was situated in the œsophagus only. Tenderness to pressure has been observed in the epigastrium and over the lower sternum; no mention is made of tender points in the back analogous to those frequently found in gastric ulcer.

The relation to food is important. As a rule, the pain occurs either during the last part of the act of swallowing or immediately afterward, in contrast to the later onset of pain in gastric ulcer. It varies from a slight burning sensation to a pain so severe as to prevent the patient from eating, and to require morphine. It is usually paroxysmal, with intervals of partial or complete relief. The passage of bougies may cause great pain.

Dysphagia: Difficulty in swallowing was present in 52 per cent. of the cases. In the early stage the method of production is as follows: the food in passing over the surface of the ulcer causes pain, which in turn by reflex action causes spasm of the œsophagus, to which the dysphagia is due. At first the patient merely experiences an obstruction at a certain point, which is soon overcome, and the food enters the stomach; later, however, the spasm is so severe that regurgitation takes place. The dysphagia and obstruction to the passage of sounds may be intermittent, probably owing to variations in the amount of spasm. In a case of Quincke, of ulcer involving both cardia and œsophagus, there was a pouch formed in the wall of the latter, which when filled with food, or entered by the sound, acted as a valve, obstructing the lumen; vomiting, however, was always possible.

Vomiting: This symptom was noted in 71 per cent. of the cases. In some cases it is due to complicating lesions in the stomach, such as ulcer, chronic gastritis, pyloric stenosis; in others it is apparently reflex, and due to the pain occasioned by the passage of food. The vomiting in some cases is of rare occurrence in others, almost incessant. It takes place usually soon after meals.

Hemorrhage: This was observed during life in eighteen cases, or 53 per cent. of the cases with a clinical history. In two others the stomach was found full of blood at autopsy, death occurring before hæmatemesis could take place. In seventeen cases the blood was vomited, in one bloody stools alone are mentioned. There were both hæmatemesis and melæna in seven cases. The blood when vomited, as a rule, presents the familiar "coffee-grounds" appearance; if the hemorrhage is profuse, however, and vomiting occurs early, it may be still a bright red. The source of the hemorrhage is found to be erosion of an artery in the base of the ulcer; in one instance (Eversmann) the aorta itself was perforated. The hemorrhage is usually repeated, and frequently profuse, causing severe anæmia. In the case of Zahn the red count fell to 950,000 and a diagnosis of pernicious anæmia was made. There is no criterion

by which one can tell, from the appearance of the blood, whether it comes from an ulcer in the œsophagus or in the stomach. Curschmann,[1] however, has noted that in hemorrhage from a ruptured œsophageal varix the blood usually gushes out without the nausea and straining which accompany gastric hemorrhage. It seems probable that this form of hæmatemesis, when accompanied by signs of ulcer, would point to the œsophagus as the origin rather than to the stomach.

Perforation: This ominous event was of quite frequent occurrence, being noted in six cases, or 14 per cent. of the total number. It was generally fatal. With perforation into the pleural cavity the patient is suddenly seized with intense pain in the chest, dyspnœa, and collapse, with the signs of pneumothorax or hydropneumothorax. The symptoms differ from those of the so-called spontaneous rupture of the œsophagus, in that subcutaneous emphysema is absent. Perforation below the diaphragm gave rise to circumscribed peritonitis of the lesser omental cavity.

Other symptoms mentioned are: dyspepsia, with anorexia, nausea, belching, pyrosis, inanition, constipation, and increased thirst.

Symptoms of the Second Stage. In those cases in which the ulceration has not been extensive this stage is not accompanied by symptoms; usually, however, the evidences of a benign stenosis of the œsophagus are present. There is a gradual onset of inability to swallow, involving first solid and then fluid food, and regurgitation takes place, at first immediately, and later, when dilatation has occurred, a considerable time after eating. With the stomach tube as much as a litre may be removed from the dilated œsophagus; that it does not come from the stomach is shown by its alkaline or neutral reaction, with absence of HCl and ferments; milk is returned uncurdled. On passing a sound an obstacle is encountered which may be impassable except for the smallest calibres.

Course of the Disease. The onset is usually gradual, beginning with pain and dysphagia; frequently dyspepsia or the symptoms of gastric ulcer precede. In other cases the ulcer remains latent up to the occurrence of hemorrhage or perforation; when ulceration takes place as a terminal event in other diseases there may be no symptoms pointing to the œsophagus. The course is often remittent, periods of comparatively good health alternating with attacks of pain, vomiting, and hæmatemesis. The duration, including the stage of stenosis, varies from a few days up to twelve years; in 63 per cent. it was under six months. Death took place most frequently from perforation or hemorrhage; other causes were inanition, perforation of other organs (stomach, gall-bladder), and chronic wasting diseases.

Diagnosis. The diagnosis of peptic ulcer of the œsophagus is difficult, and in many cases impossible; in others it may be made

[1] Deutsche med. Woch., April 17, 1902.

with a considerable degree of certainty. Peptic ulcer should be suspected in all cases with symptoms pointing to ulceration in the lower part of the œsophagus. The diagnosis is practically certain, if other causes of ulceration can be excluded, and there are dysphagia, pain during or soon after deglutition, situated under the sternum or between the shoulder-blades, hæmatemesis or melæna, and obstruction in the lower part of the œsophagus. Symptoms of present or past ulcer of the stomach or duodenum are very strong confirmatory evidence. Tenderness over the lower part of the sternum, and perhaps, also, behind near the ninth dorsal vertebra, should be looked for. Up to the present the œsophageal appearances have been recorded in but a single case, that of Starck.[1] He saw in the left anterior quadrant, 38 cm. from the teeth, a whitish ulcer with infiltrated edges and dirty, dark-red base. When touched, it bled readily, and was very painful. He made the diagnosis of carcinoma, but the complete recovery showed that he had to do with peptic ulcer. It seems probable that in the future the œsophagoscopic diagnosis will be possible for the expert, supplemented, if necessary, by excision of a piece of tissue for microscopic examination. The detection of hemorrhage may be aided by the use of the guaiac test for blood in the stools. Great care should be used in the passage of sounds, owing to the danger of hemorrhage.

Differential Diagnosis. Peptic ulcer of the œsophagus is to be distinguished from ulcer of the stomach or duodenum, and from ulcers of the œsophagus due to other causes.

From ulcer of the stomach it differs in the presence of dysphagia and in the character of the pain, which in gastric ulcer occurs at a later period after eating, and is referred to the epigastrium and lowest dorsal region, but not to the chest. Tenderness over the sternum points to the œsophageal origin; epigastric tenderness is equivocal. Ulcer at the cardia gives rise to the same symptoms as ulcer in the lowest part of the œsophagus, and cannot be distinguished from it.

Passing to the consideration of ulcers of the œsophagus which are not peptic, those occurring in the course of acute infectious diseases heal promptly, and, therefore, are not likely to cause confusion. The decubitus of the œsophagus may be seen with the laryngoscope at the level of the cricoid. Varicose ulcers are rapidly fatal from hemorrhage; they are to be distinguished from peptic ulcer by the lack of previous pain and dysphagia; the presence of signs of cirrhosis of the liver points toward a varicose origin of the hemorrhage, but is not conclusive, as two cases of peptic ulcer have been complicated with cirrhosis. The other forms of ulcer usually lead to fibrous stenosis, and will be considered later.

Stenosis following peptic ulcer is to be distinguished from the following conditions: (1) Obstruction due to compression of the

[1] See bibliography.

œsophagus from without; (2) stenosis due to causes other than peptic ulcer; (3) other diseases of the œsophagus accompanied by symptoms of obstruction.

Among the causes of compression of the œsophagus from without, the most important are aneurysm, mediastinal tumors, and cold abscesses secondary to tuberculosis of the spine. Dysphagia, usually remittent, has been met with as a rare symptom in aneurysm of the transverse arch, and of the descending aorta; perforation into the œsophagus, an unusual accident, may be preceded by marked pain on swallowing, due to ulceration of the mucous membrane. The usual signs of aneurysm, and particularly the use of the *x*-rays, will make the recognition of such cases possible. Mediastinal tumors and cold abscesses, as sources of pressure, will usually become evident on a careful examination of the chest and spine.

True stenosis of the œsophagus may be divided into two classes, malignant and benign. Of these the former is by far the more common and important. On this account, and because several of the cases of peptic ulcer have been mistaken for cancer, it will be well to go somewhat in detail into the differential diagnosis between the two. The onset in cancer is more insidious, and the course of the obstruction more progressive, without such marked intermissions as are seen in ulcer, except in those rare cases in which the passage becomes open again after the sloughing away of part of the growth. The duration is short in cancer, usually not above six months after the appearance of marked symptoms, whereas the stenosis of ulcer may last for years. In cancer the hemorrhage is smaller in amount, consisting of a little blood mixed with food or mucus; exceptionally, however, one of the large vessels may be opened, in which case death soon takes place. The pain is somewhat similar to that of ulcer, but may occur at night, and independently of the taking of food. The situation is of importance, inasmuch as the stenosis due to ulcer almost never occurs so high as the bifurcation of the trachea, the favorite seat of cancer. A high obstruction, therefore, rules out ulcer, a low one may be due to either disease. Cachexia without obstruction for liquid as well as solid food speaks for cancer (Kraus).

Further points of importance in cancer are the presence of enlarged glands in the neck, and of pressure symptoms, especially paralysis of the recurrent laryngeal nerve. These do not occur in ulcer. The examination of the stomach contents is of little assistance, as anacidity may occur with either form of stricture. Pathognomonic for cancer are the findings with the œsophagoscope, and the microscopic appearance of fragments of the growth that may be withdrawn with the sound.

Stricture due to the action of corrosive poisons is readily distinguished by the history, and the presence, at times, of scars in the mouth or pharynx. The rare strictures following typhoid fever, scarlatina, and diphtheria come on during convalescence, and, there-

fore, are not likely to lead to error. Tuberculous and syphilitic strictures are extremely rare and are not preceded by such marked pain and hemorrhage as occur in peptic ulcer. The syphilitic variety is to be distinguished from peptic ulcer by its high situation near the pharynx, the presence of tertiary lesions elsewhere, and by the improvement under specific treatment, if instituted early.

Stenosis following the ulceration due to foreign bodies is to be distinguished by the history; the presence of the foreign body may sometimes be detected by the sensation imparted on touching it with a stiff sound or by the use of the *x*-rays.

The œsophageal diseases likely to be confused with stenosis are nervous spasm, diffuse dilatation, and pulsion diverticulum. The first is usually situated at the cardia, but differs from the stenosis due to ulcer in the following points: solid food is often swallowed more readily than liquids, hemorrhage is lacking, and the obstruction, which can always be overcome by pressure, may disappear after a single passage of the sound. Signs of neurasthenia or hysteria are almost invariably present.

Diffuse dilatation which occurs as a result of cardiospasm, or of atony of the musculature of the œsophagus, may simulate stricture closely. It is recognized by the freedom with which the sound may be moved about in the œsophagus, the withdrawal from the latter of stagnating contents, in which no gastric ferments or hydrochloric acid are present, and by the œsophagoscopic findings. There is often an obstruction at the cardia, which yields when steady pressure is made.

Diverticulum is distinguished by its situation in the upper and back part of the œsophagus, the varying intensity of the obstruction, accompanied at times by a visible tumor in the neck, by the use of sounds (Leube's diverticulum sound), and by the œsophagoscopic appearances.

Prognosis. Peptic ulcer of the œsophagus is a serious affection, not only from the danger of hemorrhage and perforation, but also owing to the marked tendency to the formation of stricture, which, though often yielding readily to dilatation, is very likely to recur. Furthermore, it is often a complication of grave diseases, which of themselves bear a bad prognosis. The number of cases diagnosed during life is as yet too small to justify any conclusions as to the exact mortality.

Treatment. The indications for treatment in the stage of ulceration are the same as for gastric ulcer. In order to provide conditions favorable for healing, irritation of the ulcer by the passage of food should be reduced to a minimum. Hence, rectal feeding will be in place for a short period, with rest in bed, to be followed by a Leube cure. All articles of diet which might cause mechanical, thermic, or chemical irritation are to be avoided. The general condition of the patient should receive careful attention.

Among drugs which, when given by the mouth, may have a direct

action on the ulcer, silver nitrate ($\frac{1}{6}$ to $\frac{1}{2}$ grain, well diluted three times daily) and bismuth subnitrate (15 grains in suspension once daily) should be mentioned. It is probable that in some cases the drug will remain in contact with the ulcer long enough to exert a beneficial effect. Direct applications to the ulcer by means of the œsophagoscope probably will not be practicable on account of the danger of hemorrhage. Lavage of the œsophagus it also contraindicated for the same reason.

In the stage of stenosis, dilatation by means of bougies is usually necessary. This, in mild cases, may effect a complete cure; in others, the occasional passage of sounds must be kept up for a long time. When the stricture is impassable for sounds resort may be had to operative measures, usually gastrotomy, with subsequent feeding through the fistula. By this procedure not only is the nutrition rapidly improved, but the small ulcerations so frequently present at the stricture have a chance to heal, spasm ceases, and the œsophagus may become passable, as in Ewald's case.

In conclusion, I take pleasure in thanking Drs. R. H. Fitz, J. J. Minot, W. L. Richardson, and F. C. Shattuck, for their courtesy in placing the material at my disposal; and Drs. G. B. Magrath, F. B. Mallory, and J. H. Wright, for the use of the autopsy records.

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Table of Cases Reported Since 1878.

Group I. Ulcer in Œsophagus Only.

No.	Author.	Sex; age.	Description of ulcer.	Microscopic examination.	Lesions in other organs.	Pain.	Dysphagia.	Hæmatemesis.	Duration.	Remarks.
1	Quincke	F. 41	Girdling ulcer from cardia to bifurcation.	Excludes cancer. (Langhans.)	Cancer of ovary; cancerous peritonitis; abortion.	General abdominal.	.....	Present.	Eleven days.	
2	"	" 66	Numerous confluent ulcers in lower half; perforation into right pleura.	Excludes cancer.	Very large cyst of ovary.	.....	.....	"	A few days.	Perforation after tapping of cyst.
3	Sabel	" 32	Extensive, irregular, in lower third, exposing muscularis.	"Shows no cause for the ulcer."	Fibroma of ovary size of man's head.	Epigastric	.....	"	.....	Stools tarry.
4	Chiari	" 58	Extensive in lower half.	Excludes cancer and tuberculosis.	Incarcerated femoral hernia; perforation of bile duct; general peritonitis.	Present.	.....	.....	One week.	Blood in stomach at autopsy.
5	Shields	M. 66	Round ulcer, 1 cm. in diameter, in lower third.	.....	Chronic interstitial nephritis; cirrhosis of liver; hypertrophy L. ventricle.	In front of chest.	Inconstant.	Coffee-grounds.	Six weeks.	
6	Reher	" 47	Girdling ulcer, 4.5 cm. broad, just above cardia; scar tissue reaching to 3 cm. above bifurcation.	.....	.....	In epigastrium and lower dorsal region.	Present; obstruction 36 cm. from teeth, due to diverticulum in ulcer.	Coffee-grounds.	Four years.	Free HCl present in vomitus.
7	Lindemann	" 48	Oval ulcer, 2x1 cm., just above cardia on posterior wall; edges thickened.	.....	Double pneumothorax from perforation of ulcer; stomach normal.	Epigastric.	.....	.....	.....	Epigastric pain, like that of ulcer, for several years.
8	Carstens	F. 25	"Chronic ulceration of lower half."	.....	Tuberculosis of tubes, peritoneum, mesenteric glands; appendix abscess; pneumonia.	.....	.....	.....	.....	No history.
9	"	... ..	"Flat, peptic ulcers" in œsophagus.	.....	Marked chronic interstitial nephritis; amyloidosis.	.....	.....	.....	.....	" "

Group I. (Continued).

No.	Author.	Sex; age.	Description of ulcer.	Microscopic examination.	Lesions in other organs.	Pain.	Dysphagia.	Hæmatemesis.	Duration.	Remarks.
10	Eversmann	M. middle aged.	Extensive; beginning 3 cm. above cardia; perforation into aorta; latter not sclerotic.	Excludes cancer.	Stomach full of blood.	In the chest, on swallowing and passage of sound.	Present.	.....	Three and a half months.	Inconstant obstruction at cardia: sudden death from hemorrhage.
11	Fraenkel	M. 58	Stenosis just above cardia, with radiating scar tissue.	Excludes cancer.	.....	...	Present.	.....	One year.	Bartender.
12	Dasse	" 49	4 cm. above cardia in right postero-lateral wall, oval ulcer 2.5x 1.5 cm.	.....	Aneurysm of aorta at fourth vertebra, adherent to œsophagus.	Slight burning in œsophagus on swallowing.	.....	Profuse.	A few days.	Alcohol: "moderate."
13	Ortman	" 47	Carcinoma near cardia developing from scar of peptic ulcer.	.....	Aspiration pneumonia, with gangrene of lung.	In lower end of gullet on swallowing.	Present.	Absent.	Two years.	Dysphagia first symptom; improvement for one year with dilatation.
14	Rose	" 13	"Latent ulcer of œsophagus."	.....	Perforation into pericardium; purulent pericarditis.	.....	.....	.....	.....	No history.
15	Janeway	F. one year.	Round, 1 cm. diameter, in L. lateral wall, 2.5 cm. above cardia; periœsophageal tissue inflamed.	.....	"Infantile paralysis;" dysentery, pericarditis and pleurisy L.	.....	.....	.....	.....	No œsophageal symptoms.
16	Henoch	— five days.	Deep "ring-shaped" ulcer, 2 cm. diameter, with gray infiltrated base; situation, just above cardia.	.....	Throat normal.	.....	.....	Present, also melæna.	Two days.	Melæna neonatorum.
17	Spiegelberg	M. five days.	Pea-sized hemorrhagic infiltration with erosion at junction of œsophagus and cardia.	Shows hemorrhagic infiltration, with necrosis.	.....	.....	.....	Present, also melæna.	Two days.	Melæna neonatorum; blood cultures in life sterile.
18	Meyer	F. six days.	Small ulcer with thrombus adherent in R. wall just above cardia.	Inflammatory infiltration; streptococci present in ulcer.	.....	.....	.....	Present, also melæna.	Three days.	Melæna neonatorum.

Group II. Ulcer at Cardia.

No.	Author.	Sex; age.	Description of ulcer.	Microscopic examination.	Lesions in other organs.	Pain.	Dysphagia.	Hæmatemesis.	Duration.	Remarks.
19	Quincke	M. 42	Ulcer at cardia extending 1.5 cm. into œsophagus; longitudinal scars above ulcer.	.....	Ulcer also at pylorus; dilatation of stomach.	Present.	Present; inconstant obstruction at cardia.	.....	.....	Pocket formed at seat of ulcer, with valvular action.
20	Carstens	F. 2¾	"Large, perforating ulcer" at junction of œsophagus and cardia.	.....	Tuberculosis of mesenteric and thoracic glands, intestines, peritoneum, tubes.	.....	.....	Stomach full of blood at autopsy.	.....	No history
21	Eversmann	M. 47	Circular ulcer at cardia, extending into œsophagus and to posterior wall of stomach; scar tissue in places.	.....	Perforation of that part of ulcer lying in stomach; adhesion to left lobe of liver, with necrosis and small abscess of latter.	On swallowing.	Present.	.....	Five months.	Obstruction 42 cm. from teeth; perforation after sounding; clinical diagnosis, cancer.
22	Krokiewicz	" 46	Ulcer at cardia, extending into anterior wall of œsophagus.	.....	Ulcers also at pylorus and lesser curvature; stomach dilated.	Between shoulder-blades.	Present.	Present.	Four weeks.	Free HCl increased; absent later.
23	Zaleski	" 39	Irregular ulcer of lower third of œsophagus and cardia, extending a short distance into stomach.	.....	Scar of ulcer at pylorus with stenosis; dilatation of stomach; pulmonary tuberculosis.	Severe in epigastrium and lower sternum, radiating to back between shoulder-blades.	.....	Present and cause of death.	Three months.	Free HCl diminished.
24	Fraenkel	" 47	Ulcer 4.5x6 cm. at junction of œsophagus and cardia; scar tissue in the base.	Chronic inflammatory tissue; gastric glands present in œsophagus.	.....	Severe, epigastric, with tenderness.	.....	Present.	Five months.	Free HCl present, 0.18 per cent.

Group III. Complicating Ulcers in Other Parts of the Stomach or in the Duodenum.

No.	Author.	Sex; age.	Description of ulcer.	Microscopic examination.	Lesions in other organs.	Pain.	Dysphagia.	Hæmatemesis.	Duration.	Remarks.
25	Quincke	M. 50	Stenosis due to contracted scar at lower end of œsophagus; hypertrophy above.	Inflammatory infiltration.	Scar of ulcer on posterior wall of stomach.	.....	Present.	.....	.....	Gastric symptoms for "a considerable time."
26	Debove	" 55	Stenosis 5 cm. above cardia, due to scar; typical fibrous radiations.	.....	Perforation of ulcer of anterior wall of stomach.	Epigastric, and at xiphoid, radiating to shoulder and eighth dorsal vertebra.	Present.	Present; repeated.	Five years?	Symptoms of gastric ulcer; eighteen years relief from dilatation; drunkard.
27	Zahn	" 46	Ulcer in lower œsophagus, with hypertrophy above.	Small-cell infiltration; thrombosis of an artery.	Ulcer of duodenum; dilatation of stomach; cirrhosis of liver.	Severe; epigastric.	.....	Present; frequent.	Six weeks+	Drunkard; red cells, 950,000.
28	Vulpian	" 63	Six ulcers in lower fifth, involving almost entire circumference.	.....	Smaller, shallower ulcers near pylorus.	Severe, epigastric of sudden onset.	Absent.	Absent.	Two months.	Severe dyspepsia five years before.
29	Ewald	" 30	Round; 3 cm. diameter, on R. wall just above cardia; perforation into lesser omental cavity.	Excludes cancer.	Duodenal ulcer with stenosis; pulmonary tuberculosis; localized peritonitis.	Severe epigastric, referable to duodenal ulcer.	.....	Frequent.	Thirty days.	Free HCl present; stomach dilated.
30	Fraenkel	... ...	Round, with sharp, raised edges and funnel-shaped base, in lowest part of œsophagus.	.....	Similar ulcer in duodenum.	.....	....	.....	.....	Museum specimen of Rokitansky.
31	Kraus	M. 59	Girdling; extending 6 cm. upward from cardia.	Inflammatory infiltration, extravasation of blood.	Ulcer at pylorus; enormous dilatation of stomach.	.....	.....	.....	.....	Stools bloody.
32	Kraus	" 24	Numerous; confluent, extending to muscularis, situated in lower œsophagus; latter dilated.	Small-cell infiltration and extravasation of blood.	Scar of ulcer at duodenum, with stenosis; hour-glass stomach, with dilatation.	Epigastric, very severe.	.....	Repeated: profuse.	.....	
33	Hödlmoser	" 35	3.5 cm. in diameter; in lower end of œsophagus; anterior wall.		Two duodenal ulcers, with stenosis, and dilatation of stomach; hypoplasia of aorta.	At lower end of sternum; increased on taking food; tenderness.	Present.	Profuse; causing death.	Six weeks.	Symptoms of gastric ulcer five years before.

Group IV. Cases without Autopsy.

No.	Author	Sex; age.	Description of ulcer.	Microscopic examination.	Lesions in other organs.	Pain.	Dysphagia.	Hæmatemesis.	Duration.	Remarks.
34	Debove	M. 54	Two stenoses: (1) near cardia; (2) at level of top of sternum.	.....	.....	At sternum and between shoulder-blades.	Present.	Present; coffee-grounds.	Twelve years.	Alcoholic patient; cured by dilatation; no signs of syphilis.
35	Ortmann	" 27	Obstruction 40 cm. from teeth.	.....	Stomach reaches 3 cm. below navel.	Epigastric.	Present.	Present.	Five years.	Sudden onset of dysphagia and pain; cured by dilatation.
36	"	" 30	Obstruction 43 cm. below teeth.	.....	Stomach three fingers below navel; phthisis, third stage.	.....	Present.	.....	Four years.	Improved by dilatation.
37	"	F. adult.	Obstruction 32 cm. from teeth.	.....	.....	Paroxysmal at middle of sternum.	Present.	.....	Several years.	Diagnosis by Quincke; improved by dilatation.
38	"	M. 42	Obstruction 42 cm. from teeth.	.....	Ptosis of stomach.	At xiphoid.	Present.	Present.	Five years.	Free HCl present; relief from dilatation.
39	"	" 28	Obstruction 43 cm. from teeth.	.....	Ptosis of stomach.	At xiphoid on swallowing.	Present.	Absent.	Five years.	Onset with violent pain in chest and stomach, after drinking sour wine; improved by dilatation.
40	Ewald	F. 19	Impassable stricture 30 cm. from teeth.	.....	Partial stenosis of pylorus.	At xiphoid on swallowing.	Present.	Absent.	Two months.	HCl increased; partial recovery after gastrostomy.
41	Starck	" 60	Ulcer, with dark red base and infiltrated edges, in left anterior quadrant, 38 cm. from teeth (œsophagoscope)	.....	.....	Between shoulder-blades.	Present.	.....	Nine months.	Recovery.

PRIMARY SARCOMA OF THE ADRENAL GLAND.

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Primary malignant tumors of the adrenal glands are sufficiently rare to give interest to the report of a case which came under my observation at the postmortem examinations of the present year; and, in connection therewith, to refer to a similar case reported in the *Journal of the American Medical Association*, 1888, vol. x. Some additional interest is attached to these cases, as in neither were there any symptoms of Addison's disease.

Ramsay, in an excellent article in the *Johns Hopkins Hospital Bulletin*, 1899, vol. x., has collected from literature and studied sixty-seven cases of primary malignant tumors of the adrenals, three of which were his own. To this article I shall frequently have need to refer, and here acknowledge my indebtedness.

The difficulty of clinical diagnosis of tumors of the adrenals, especially those without skin affection to suggest them, was in my two cases increased by the mental condition of the patients, both of whom were demented. It is only fair, however, to state that in the first case tumor of the abdomen was recognized during life; and that in the second case malignant growth of some kind was suspected from the symptom-complex, and from the chemical and bacteriological examination of the stomach contents, though the supposed location of the growth was found to have been incorrect. For the brief history of my first case and the details of the postmortem notes, I would refer to the original article; I reproduce, however, two photographs of the gross specimen (Figs. 1 and 2). The following is the recorded history of the present case, for which I am indebted to my colleague, Dr. H. R. Hummer, in whose service the case occurred.

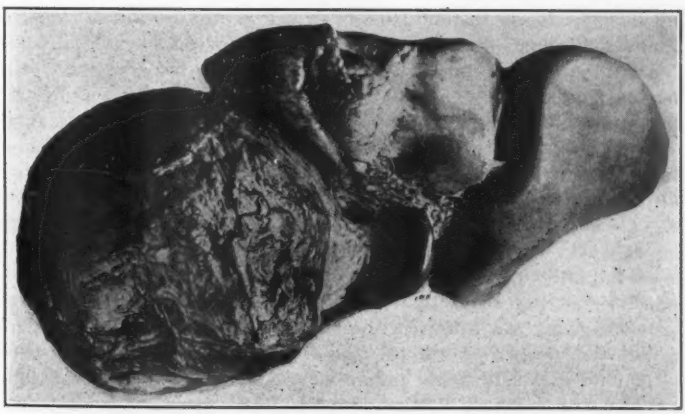
Case No. 12,570. L. S.; male, aged seventy-eight years, white, late soldier; nativity, Ohio. Mental disease: senile dementia, duration about sixteen years. Admitted to the Government Hospital for the Insane June 28, 1901.

The history obtained on admission states that the patient was at times emotional and abusive, and was delusional. Later on loss of memory for recent events was a prominent feature, and he was violent in temper, quarrelsome, and threatened his attendants. On admission to this hospital, physical examination showed some enlargement of the heart and a mitral regurgitant murmur; the mental reactions were sluggish; it was apparently a simple case of senile dementia. On July 29, 1901, he fell and sustained a

FIG. 1

A section of the adrenal tumor (Autopsy No. 203) removed by the writer postmortem, and reported in the Journal of the American Medical Association in 1888. This tumor was about the size of an adult head and weighed 2757 grams. The histological structure was almost identical with the second tumor reported herewith, but it was not pigmented, and there were no metastases.

FIG. 2



View of the tumor shown in section in Fig. 1, showing the size of the growth relative to that of the liver, the under surface of the latter being shown.

fracture of the right femur near, or within the hip-joint, after which he was obliged to remain in bed. In bed the patient slept well, was quiet, and did not complain of pain; no union of the fractured bone took place, though the acute symptoms duly subsided.

From the above date until October 12, 1904, the progress of the case presented nothing of especial note. At this time it was observed that the patient was rapidly losing weight, having fallen off six and three-quarter pounds in three weeks.

October 15th, the injured limb began to swell, and at this time urine analysis showed purulent cystitis. October 27th, he refused nourishment, saying that his stomach was decayed. He had grown emaciated; his pulse was rapid and weak; urine scanty and purulent at times; and he began to groan distressingly, but whether from actual pain or not could not be determined owing to his mental condition.

From the time of the onset of these graver symptoms he took but a little liquid food, and that only with much persuasion. Suspecting some disease of the stomach from the fact that he vomited occasionally, a test-meal was attempted, but could not be given.

November 19th his stomach was washed until clear water returned, and on the 22d he was given the test breakfast through the stomach tube and the contents therewith withdrawn. The material from the stomach was examined and hydrochloric acid was found to be absent; lactic acid was present; and the Oppler-Boas bacilli were found; suggesting carcinoma of the stomach, though the more characteristic symptoms were absent.

The patient had continued to lose flesh rapidly, having lost twenty pounds in less than two months. He had some cough and loose bronchial rales, but was too weak to expectorate, and dulness began to be distinguishable in the posterior portion of both lungs. Sputum for examination could not be obtained. The temperature had occasionally reached 100° F., but was usually subnormal; pulse always about 100 to the minute; respirations 27 per minute, becoming much more rapid a day or two before he died.

During his last illness repeated examinations of the abdomen failed to elicit any pain, and no tumor could be felt. The skin had apparently a slightly increased yellowish tint attributed to hæmatogenous jaundice or cachexia, but no bronzing of the skin could be detected.

In the latter part of his illness the secretion of urine had become scanty, sometimes less than two ounces in twenty-four hours; the prostate gland was known to be enlarged, and in the semipurulent urine were numerous minute calculi or gravel. The patient died of general exhaustion and pulmonary œdema, November 23, 1904.

From the synopsis of the clinical history it may be seen that the patient had some of the symptoms which may be considered as characteristic of adrenal tumor, though certainly not sufficient

for diagnosis of the condition in the absence of palpable tumor and bronzing of the skin. Pain of indefinite character was undoubtedly present toward the last, but it could not be located nor elicited by abdominal palpation. Marked and steadily increasing weakness, rapid emaciation, anæmia, loss of appetite, and digestive disturbances were noteworthy. Circulatory disorder was indicated by rapid pulse, weak cardiac action, and œdema of the legs. The temperature was at times slightly above the normal, but was at other times subnormal, the slight rise being probably influenced by the bronchial inflammation. Hæmaturia was never observed though the calculous disease might of itself have caused it.

Tumor of any kind might not have been suspected if the stomach derangement and other symptoms had not suggested gastric tumor, and the examination of the contents of the stomach apparently confirmed the diagnosis of cancer.

It is interesting to note in this connection that the researches of Professor B. Moore (*Proceedings Royal Society*. May 24, 1905) show that in malignant disease of any organ there is marked diminution of free hydrochloric acid in the stomach in all cases below 1 per cent., or else an entire absence of this substance. The knowledge of this fact, however, while it would have in a measure strengthened the diagnosis of tumor, could have in no way aided in localizing the growth in the adrenal gland.

It is well known that HCl may be absent in chronic atrophic gastritis, but lactic acid is apt to be absent also, therefore the combination found in our analysis of the test-meal material was to say the least unusual and misleading.

Autopsy (No. 1914). Examination fourteen hours after death. Body, though it has evidently lost much superficial fat, is still not greatly emaciated. The skin shows the usual death pallor, but no pigmentation nor other pathological condition can be noticed. The usual evidences of fracture of the femur at the right hip joint are noted.

Cranium. Skull normal; dura adherent to the bone.

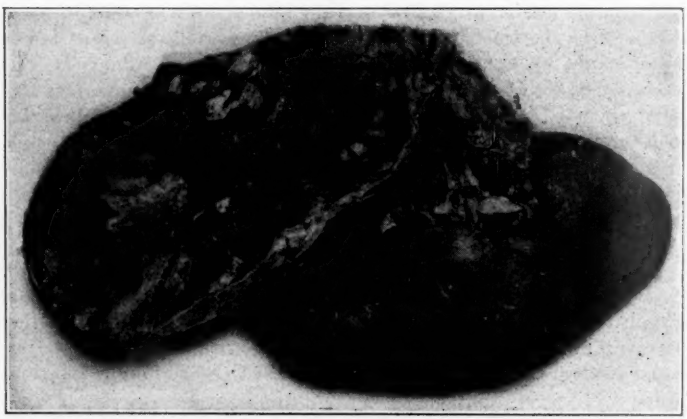
Brain weight: 1240 grams. Pia œdematous and slightly opaque; convolutions considerably atrophied. Arteries at the base show some patches of sclerosis and are a little more tortuous and irregular in calibre than normal. Section of the organ shows nothing abnormal in the interior except slight œdema.

Thorax. The right lung is adherent posteriorly and shows some hypostatic exudation; the surface is studded over with small rounded nodules, varying in size from a microscopic granule to a node about 2 cm. in diameter. Section shows the parenchyma of the lung full of nodules of similar sizes, and uniformly distributed. The nodules are grayish red in color, and some are slightly mottled with dark pigmented areas. They are moderately firm, usually round, and each nodule remains distinctly circumscribed. The left lung

is free from pleural adhesions; it presents the same general appearance as the right and contains great numbers of similar nodules, except that some of the subpleural nodes of the larger size at the lower margin of the lung have become pedunculated. Section of the lung tissue shows partial solidification of the posterior portions of both; some carbon pigmentation, and some mucopurulent secretion in the bronchi. The left lung weighs 560 grams, the right, 730 grams.

Heart. Weight 420 grams. The organ is slightly dilated and is relaxed. Pulmonary valves normal; tricuspid orifice slightly stretched and probably was incompetent, but the segments are normal. Aortic valves are a little thickened and calcareous; mitral valves slightly thickened, but probably competent. Lower part of the aortic arch sclerotic and calcareous, and some patches are found at the lower part of the vessel.

FIG. 3



The tumor of the right adrenal gland (Autopsy No. 1914), sectioned in the middle to show its structure and shown in relation to the kidney, which it nearly equals in size. The section shows the appearance of the tumor tissue, the interior broken down by degeneration, and the more solid tumor tissue mottled by hemorrhage and pigmentation. The capsule is seen to be very distinct, but no septa enter the tumor, the appearance of such being the looser, more degenerated portions of the tumor between the more actively growing centres. The kidney shows a slightly granular surface, indicating some interstitial change, but no secondary tumor growths are seen on the surface shown.

The walls of the heart contain numerous nodules of a grayish red color, slightly mottled with brownish pigment areas, some of which are about one and one-half cm. in diameter, some of minute size. They are found in all parts of the heart, but are most numerous in the walls of the ventricles. On section they are rounded in form, some lie immediately beneath the epicardium and project

slightly beyond the general surface, and some lie deep within the myocardium.

Abdomen. No increase of abdominal fluid; some small tumor nodes noted on inspection of omentum and mesentery.

Spleen. Weight, 320 grams. The capsule shows a number of patches of cartilaginoid tissue, some of which are calcified. The pulp is soft, otherwise nothing abnormal is noted on section.

Kidneys. On attempting to remove the right kidney it is found to be in close relation with a soft tumor about the size of the kidney and occupying the position of the adrenal gland. Both kidney and tumor are embedded in perinephritic fat, and are removed together. The tumor is ovoid in shape, soft, almost fluctuant, and evidently takes the place of the adrenal gland. The ascending vena cava lies in close relation to its inner border, and a vein, probably the adrenal, enters the tumor (Fig. 3).

The tumor is 12.50 cm. in length; 6.50 cm. in breadth, and somewhat less in thickness. The kidney and tumor together weigh 500 grams; probably each weighs 250 grams, as they were not separated. Section through the growth made parallel with the anterior face of the kidney shows a softened hemorrhagic tumor the central portions of which are much broken down and filled with thin bloody fluid. The more consistent tissue is grayish red in color, mottled with blackish pigment, and the central portion consists of shreddy blood-stained tissue and semicoagulated blood. The ascending vena cava contains nothing abnormal, and the vein which enters the tumor is pervious, and is lost in the tissue. To the naked eye no trace of adrenal tissue can be seen, and the capsule of the gland seems to have been enlarged and greatly thickened to form the limits of the new-growth.

The kidney is preserved entire with the tumor; a few whitish nodules are seen in the cortex, the capsule adheres slightly, and the surface is faintly granular. The perinephritic fat contains a few grayish-red nodules, probably secondary tumor deposits.

The left kidney and its adrenal gland are next examined. The kidney weighs 200 grams; in appearance it is the same as the right, and like it contains a few small tumor deposits. The left adrenal gland is found to be enlarged and a transverse section reveals a rounded tumor mass about 3.5 cm. in average diameter. The tissue of this tumor is grayish red in color and there remains between it and the capsule of the gland a thin yellow line of tissue, the remnant of the adrenal gland. The tumor occupies the central portion of the gland, the extremities being uninvaded.

The ureters are a little dilated. The bladder is slightly dilated and shows traces of chronic catarrh and numerous small calculi, some of which are about the size of a pea.

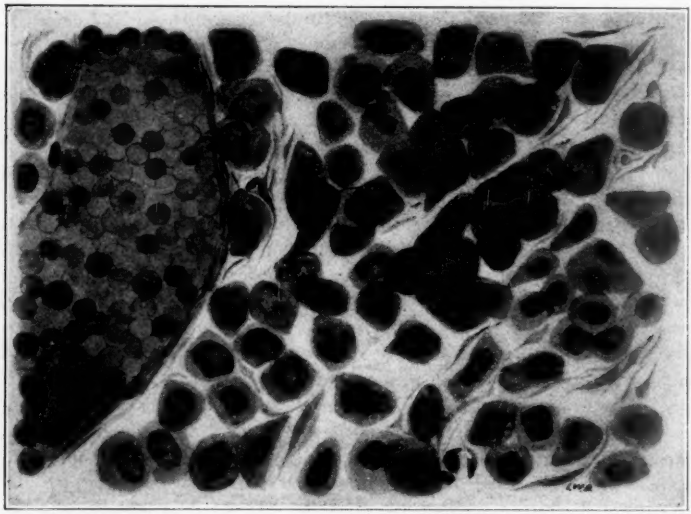
The liver weighs 1560 grams. It contains a few small secondary

tumors, of whitish color, the largest being in the anterior border of the left lobe. The liver tissue, the gall-bladder, and biliary ducts seem normal.

The pancreas is sectioned lengthwise and found to contain a few nodules of tumor deposit in the caudal portion, recognized by their color and slight pigmentary deposits. The peripancreatic fat, the mesocolon, and mesentery contain a few small tumor nodules.

The stomach is dilated and the mucous membrane is coated with tough mucus. A small ulcer of uncertain character occupies the upper part of the duodenum, about an inch from the pylorus. No secondary tumor deposits in any part of the alimentary tract, and the ulcer is not cancerous.

FIG. 4



Structure of tumor in Autopsy No. 1914. Actual field drawn with the camera lucida. Leitz $^1/_{12}$, ocular No. 3. The field drawn shows the arrangement of the cells, the scanty intercellular substance, faintly granular condition of some of the cells, the prominent nuclei, and a large sarcomatous bloodvessel with eosin-stained red cells and a few leukocytes of various kinds. From a secondary nodule in the lung. (Reduced.)

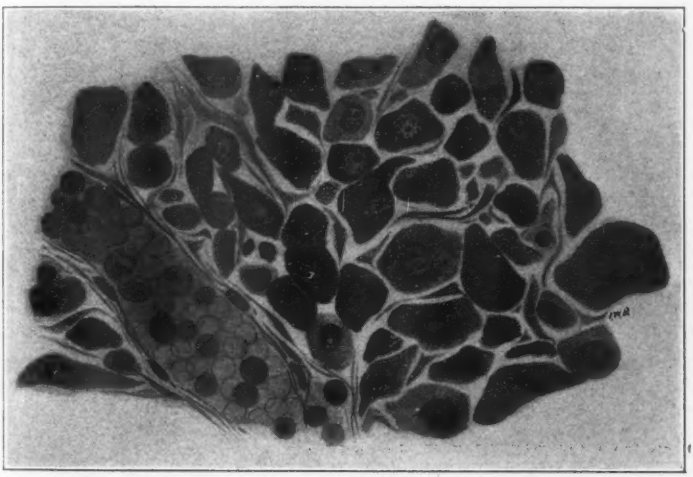
The head of the femur is found to be bound to the shaft by the capsule of the joint, the periosteum, and some fibrous tissue. The neck of the bone is nearly gone and the head lies at right angles to the shaft, and the trochanter major lies against the acetabulum. The diagnosis of this injury is intracapsular fracture of the femur.

The pathological diagnosis from the gross appearances of the growths is primary melanotic sarcoma of the right adrenal gland, with extensive metastases, involving the left adrenal, lungs, heart,

liver, kidneys, pancreas, peripancreatic and perinephritic fat, omentum, mesentery, and mesocolon.

Microscopic Examination of the Tumor. The predominating types of cells are shown in Fig. 4. They are usually more or less polygonal by mutual pressure, though where the tissue is less dense they assume the rounded form. The cell-bodies stain lightly in hæmatoxylin and eosin, and even with the highest amplification are only occasionally faintly granular. They vary in size within narrow limits, even in the typical parts of the tissue; but in the secondary nodules and regions in which degenerative changes are taking place they differ greatly in size and shape, as shown in Fig. 5 and in Fig. 6, which shows the great variety in size, shape, and

FIG. 5



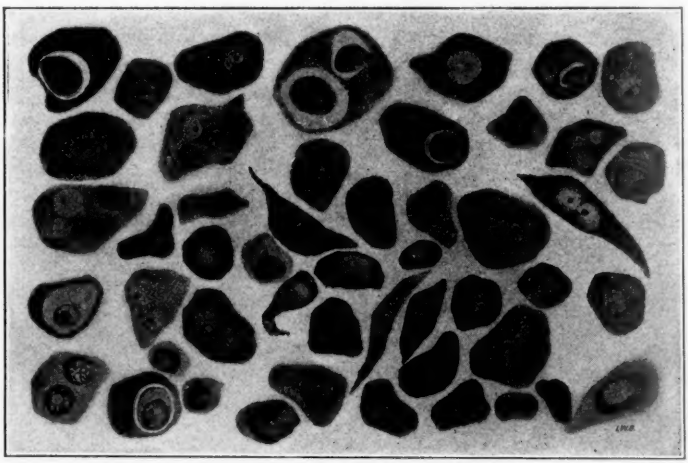
Field drawn from a secondary nodule in the lung, showing enlarged and pigmented cells with degenerated nuclei. The great irregularity in size and form of the tumor cells, their shapes influenced by mutual pressure, the delicate intercellular substance, and some enlarged and vacuolated nuclei are shown; and a sarcomatous bloodvessel with eosin-stained erythrocytes, lymphocytes, and polymorphonuclear cells filling the lumen, and flattened endothelium and a few strands of delicate connective tissue forming the wall. Leitz $^1/_{12}$, ocular No. 3. (Reduced.)

degenerative changes in cells collected from various secondary nodules in the lungs. It is noteworthy that many small, more or less rounded cells, with nuclei as large as those of the larger elements, and relatively little cell protoplasm, lie in the midst of the cells of large size and varied shapes. These are probably young cells, as they are more numerous in the growing portions of the tumor, and among the cells invading the tissues in the vicinity of the secondary deposits. Many elongated or spindle cells are found

among those of other shapes, and entering into the formation of indistinct alveoli in some parts of the tumor; but these cells form a very unimportant feature of the structure and alveolar arrangement is only occasionally demonstrable.

A marked peculiarity of growth is seen in some parts of the tumor, and in some of the secondary nodules. This is the arrangement of the tumor cells into elongated trabeculæ, or rows two or three cells wide, strongly suggesting the normal structure of the zona faciculata and zona reticularis of the adrenal gland. Sometimes capillary bloodvessels can be demonstrated between these rows of cells, which further suggests the normal structure (Fig. 7). This in my opinion is an evidence of the origin of the tumor cells from

FIG. 6



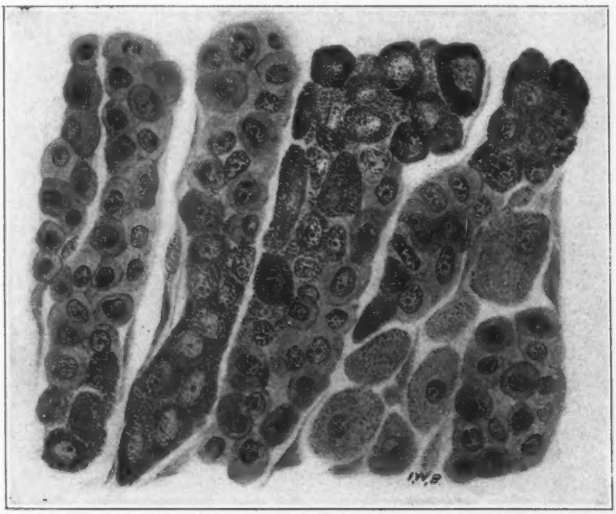
In this plate have been collected a number of cells from various fields of secondary nodules of the lungs. Almost all of the types of normal and degenerated tumor cells are here represented. Vacuolation of the cells and their nuclei, and pigmentation in various stages are shown, cells of bizarre forms and a number of so-called "cell inclusions" known to the older pathologists as endogenous cells or "daughter cells." Almost every phase of nuclear degeneration and cytoplasmic pigmentation is represented. Drawn with camera lucida. Leitz $^1/_{12}$, ocular No. 3. (Reduced.)

the epithelial elements of the adrenal, the cells following the law of hereditary resemblance to the parent tissue well recognized in neoplastic growths.

The nuclei of the cells present more uniformity in size and structure, except when they are altered by degeneration. They are quite distinctly stained by ordinary nuclear stains, show a coarse intranuclear reticulum, limited by a distinct nuclear membrane, and contain as a rule one or more prominent nucleoli. The nuclei

almost exactly resemble those of the adrenal epithelium. In fields where the pigmentation and degeneration of the cytoplasm are evident the nuclei show most marked difference in size, and share in the degenerative processes. Vacuolation is common, sometimes occupying the whole nucleus; the nuclei are frequently divided into two or more vacuole-like bodies, each containing a nucleolus; and occasionally minute vacuoles. A few cells contain two nuclei in close proximity indicating nuclear division; a few have three or four nuclei, usually smaller than the common single forms; and occasionally the partial division of the cell-body indicates direct cell multiplication, but no distinct evidence is seen of indirect cell

FIG. 7



Field from the primary tumor of the right adrenal gland from the periphery of the growth near the capsule. Several trabeculæ of cells, from two to three or four cells thick, extend in parallel rows, strongly suggesting the normal gland. Spaces, in some instances found to be capillary blood channels, are seen between the rows of cells. At the lower right corner are several larger cells and cell-fragments which are adrenal cells crowded together, compressed and degenerated by the advance of the tumor elements. Leitz $^1/_{12}$, ocular No. 3. (Reduced.)

division or karyokinesis. Quite a number of the so-called "cell inclusions" are found; in some cases the cell contains a clearly defined "daughter cell," which is separated from the inclosing cell by a clear space, and stains more distinctly; in addition its own nucleus is either normal or more or less degenerated. Several of these ill-understood elements appear in Fig. 6, which also shows a remarkable collection of cells and nuclei in various stages of retrogressive change and pigmentation.

The pigment seems to be very irregularly distributed, and by

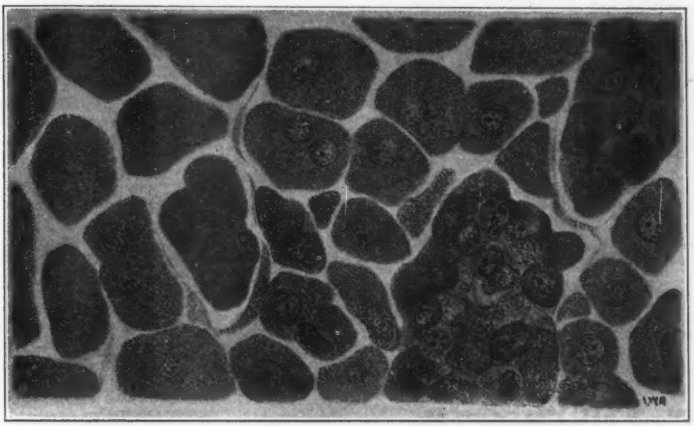
far the greater number of the cells are unaffected. In some parts of the primary tumor, and in many secondary nodules, pigment is absent, but when present all kinds of cells are affected. Sometimes a single pigmented cell, or a group of two or three, may be found isolated in the midst of an entire field of non-pigmented cells. In some of the trabeculæ or rows of cells a portion may be pigmented, while the remainder is unchanged. So far as can be determined the pigment is confined to the protoplasm of the cells, and the nuclei stain a pale rose tint in eosin, while the cytoplasm may be completely filled with yellow pigment granules. In some cases the pigment has accumulated until the nuclei are obscured, but apparently not pigmented, or at least not granular. In the degenerated nuclei in which the intranuclear reticulum has disappeared, the nuclei are yellow and ill defined owing to the degeneration of the surrounding cytoplasm.

It is difficult to describe the pigmentation of the cells. The alteration exists in all degrees from the faintest yellowish tint, which causes the cell-body to assume a salmon pink hue when stained, to a deep yellow color, with brownish-yellow granules. It is more difficult to decide as to the true nature and origin of the pigment. To the ordinary tests, and in microscopic and macroscopic appearances it answers to melanin; and when tested with hydrochloric acid and ferrocyanide of potassium it is found to contain no iron. It may be a direct transmission of the metabolic pigment-forming function of the cells of the zona reticularis of the adrenal gland; in which case it would be some evidence of the derivation of the tumor cells from the epithelial cells of the gland; or it may be in part a degenerative change in the tumor elements, as the pigmented cells are more apt to assume unusual form and size, and the nuclei of these cells are more commonly degenerated.

In the right adrenal tumor the pigment is in streaks and patches; in the left adrenal the cells are but little pigmented; in some of the secondary tumors the pigment is absent, and in some of the pulmonary nodules the cells are nearly all pigmented and in others the pigment is scanty. Though irregularity in pigmentation is common in tumors of this class, I have thought it possible that the tumor cells were derived from more than one zone of the cortex of the adrenal gland primarily affected. The cells of the zona glomerulosa and the zona fasciculata are not pigmented; the cells of the zona reticularis are so normally, and the pigment much resembles that of the tumor cells. The medullary cells are of doubtful embryogenesis, and may be thought of as sources of abnormal growth, but these cells are not pigmented. The natural conclusion is that the tumor cells are derivatives from the adrenal cells of the zona reticularis, and possibly the other cortical zones of the adrenal primarily affected, and this was apparently the right gland.

Sections from the *primary tumor* were studied in connection with those found in other organs, and as is the rule in secondary tumor growths, the neoplastic tissue everywhere was found to be remarkably uniform in structure. The tissue in the right adrenal had degenerated more than in the secondary nodules, and, therefore, the more minute details were better studied in these, especially in those of the lung. The mode of invasion of the adrenal tissue itself could only be studied in the left gland, as only microscopic remnants of the right adrenal tissue remained. Sections were examined from all the affected organs, revealing some peculiarities of growth, which may be given in detail.

FIG. 8



Field from the advancing border of the nodule in the left adrenal gland, showing portions of four clumps of tumor cells lying in the midst of the adrenal cells remaining near the capsule. The tumor cells stain more deeply than the adrenal elements, and they are seen to lie in compact masses apparently without intercellular spaces, and the individual cells are hard to outline; whereas, the adrenal cells do not lie in contact in this field, though no intercellular substance can be demonstrated. It is probable that in many instances these intercellular spaces are artificially produced during preparation of the tissue. The adrenal cells are granular and in places compressed; the tumor masses stain a little darker and are therefore easily distinguished. Leitz $^1/_{12}$, ocular No 3. (Reduced)

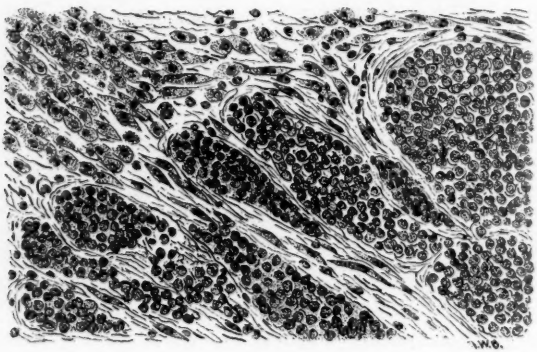
I should conclude from the gross appearance that the tumor mass in the *left adrenal* was probably secondary and that the invasion of the tissue was from within outward. The microscopic study seems to confirm this, as a narrow line of adrenal tissue yet remains between the tumor mass and the capsule. Between the two there is a region where the tumor cells have insinuated themselves between the adrenal elements and have compressed these cells into elongated spindles, the nuclei having as a rule retained their size and shape (Figs. 8 and 9).

In some fields of this tumor the cells are arranged in elongated alveoli which I have mentioned elsewhere as suggesting the mode of growth of the normal gland. In other fields the alveolar arrangement is more like that of ordinary alveolar sarcoma, and on the border-line the tumor cells often lie isolated among the adrenal epithelial elements, from which they can with some difficulty be distinguished.

The tumor masses as a rule stain slightly deeper in nuclear stains, and the cells are a little smaller and more densely aggregated than the surrounding adrenal cells. Pigmentation is not a marked feature in the tumor of the left adrenal; otherwise it much resembles the growth in the right, but the tissue is less degenerated.

The nodules in the *heart* are practically identical in structure with that of the left adrenal. The pigmented cells are rather more common, and have the same irregularity of distribution as noted

FIG. 9



A low-power view, showing the encroachment of the tumor cell-masses upon the remaining adrenal tissue of the left adrenal and the compression of the epithelial cells into spindle shapes. × 200.

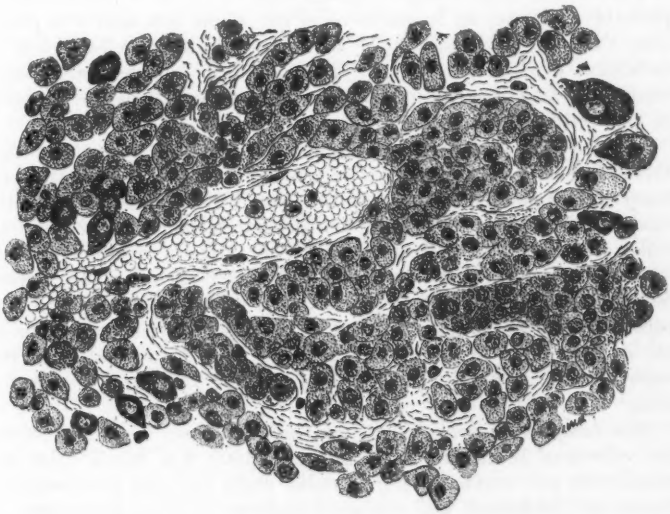
elsewhere. Where the heart muscle lies adjoining, the tumor cells are found between the more or less compressed muscle fibres. Where the tumor masses have expanded laterally the muscle fibres are so flattened as to be scarcely recognizable. Where the connective tissue of the intermuscular septa forms the boundary of the tumor the sarcoma cells are seen to fill the lymph spaces, lying in elongated rows. In cases where the nodules are adjoining the epicardium a layer of muscle tissue has been carried in advance and become compressed against the connective tissue.

The muscle cells of the myocardium in general show a slight degree of pigmentation in the vicinity of the nuclei, but are otherwise normal.

In the *pancreas* the secondary deposits have the same character as elsewhere and are found in the connective tissue of the gland. The larger nodules have compressed the glandular tissue in the vicinity; in other respects the gland seems normal.

The *liver* nodules show the typical structure of the primary tumor, though very few pigmented cells are found. The tumor cells are quite uniform in size, polymorphous from pressure, and in some fields a tendency to alveolar arrangement is seen, and in the thinner portions of the sections some grouping of the cells

FIG. 10



This figure represents a field from a secondary nodule of the lung, showing the tumor cells arranged in trabeculæ, suggesting the structure of the adrenal gland; a large sarcomatous bloodvessel; the general structure of the secondary growths; and a few pigmented cells. × 300.

(These drawings were done with the camera lucida to secure the cell outlines. The stippling is used for shading and not to represent the protoplasmic structure. Pigmentation is represented by heavy granular shading to secure the general effect.)

around the bloodvessels. In most cases a distinct connective-tissue capsule limits the growth, and occasionally the tumor cells have penetrated the boundary and invaded the spaces between the liver cells. In the vicinity of the larger nodes the hepatic cells are compressed into spindle shapes, and degenerated; more remote from the growths these cells show a few pigment granules, and some contain fat globules from infiltration.

The secondary nodules in the *omentum* and *mesentery* present the same general structure as elsewhere, and need not be separately

described. The same may be said of the *renal* deposits. The kidney tissue shows slight interstitial increase and some cloudiness of the epithelium.

The secondary tumor nodules in the *lungs* present wide differences in the degree of pigmentation and degeneration of the cells, and in the details of structure of the tumor tissue. In some nodes the cells are quite uniform in size and shape, and are devoid of pigment, while perhaps in an adjoining nodule the cells are found of the most varied shapes and sizes, and show every degree of pigmentation and degeneration (Figs. 4 and 5).

The nuclear degeneration so pronounced in some of these nodules probably indicates an impairment of the whole cell, and it is probable that the proliferation of the nuclei without cell-division is indicative of the same thing. Quite a number of cells are found containing two or more nuclei with, in some cases, partial division of the cell-body.

In some fields a marked tendency is seen for the cells to arrange themselves in elongated rows, suggesting the structure of the primary tumor and the adrenal gland (Fig. 10). These clumps and rows of cells take the staining a little better than the surrounding cells, and are thus differentiated. The sarcomatous bloodvessels in the lung nodules are large and full of blood, and show imperfectly developed walls (Figs. 4, 5, and 10). Some secondary nodules, especially in the lungs, are remarkably vascular, and occasionally the cells grouped in the vicinity seem to have some relation to the vessel walls, probably proliferation nearest the supply of nutrition.

The *lung tissue* included in the tumor sections examined shows the effects of bronchitis and peribronchitis. The bronchioles are filled with pus exudate, the alveolar walls and the peribronchial itssue are thickened, and coal-dust pigment is found in clumps in the connective tissue. Small collections of lymphoid cells are found here and there, indicating active interstitial inflammation. The alveoli contain leukocytes, epithelial cells, and some cells filled with black pigment granules—"dust cells." The bloodvessels of the lung tissue are engorged and some contain dark pigment granules of uncertain origin, possibly sarcomatous pigment.

Some of the lymph spaces in the vicinity of the tumor nodules contain sarcomatous cells and around the larger nodes the lung tissue is compressed.

CONCLUSIONS AS TO THE DIAGNOSIS AND NATURE OF THE TUMOR. Primary tumors of the adrenal glands are sarcoma, carcinoma, adenoma, hypernephroma, and, more rarely, glioma, ganglionic neuroma, and endothelioma. Of the primary malignant tumors those commonly recognized are sarcoma in its various forms and carcinoma; and to these we must add malignant hypernephroma; and, according to Prudden, "certain large vascular and hemorrhagic adeno-

mata which may invade the neighboring vessels and form metastases."

Sarcoma is said to be much more frequent than carcinoma, though in the sixty-seven cases collected by Ramsay thirty-seven were carcinoma and thirty sarcoma. It is highly probable that careful histological study would greatly alter these figures.

Primary sarcoma of the adrenal must originate in either the connective tissue of the gland or the epithelium. The latter being of mesodermic origin according to the best authorities, would be histogenetically capable of forming a sarcoma, and if such origin be established we have a tumor not differing in embryogenesis from ordinary sarcoma, though derived from mesodermal cells which have undergone marked morphological differentiation.

If carcinoma be derived from the adrenal gland it must originate from the epithelial elements, while the connective tissue of the gland forms its stroma; or have an origin in misplaced tissue of other blastodermic layers. It is hard to conceive how the same histological elements can give rise to tumors of widely different character; but the same difficulty arises in case of these tumors in any of the mesodermic epithelial structures. Carcinoma of the kidney is comparatively rare, and Prudden says carcinoma of the adrenal is not common. It is indeed probable that many cases of malignant tumor of these mesodermic glands are histologically, as well as embryologically, more closely related to the sarcomata than to the carcinomata. In my opinion the establishment of the histogenesis of any given tumor is of more importance than the sometimes forced assignment of the growth to any arbitrary class. The tumor under consideration presents marked characteristics of structure which indicate that it was a development from the adrenal epithelial cells, rather than from any other constituent of the organ. It does not present the characteristic structure of any form of cancer, and while it preserves to a degree the normal histology of the gland sufficiently to merit the term adenoid, it is certainly not an adenoma.

The gross appearance of the tumor and the histological structure are not those of hypernephroma, as usually described and figured by authors and studied also by me. In no part of any of the tumors is there any acini-like structure, with open alveoli (sometimes filled with blood), and with walls lined with more or less columnar or cuboidal cells resting upon the capillary walls, such as appears to be characteristic of hypernephroma. The cells are not fatty, and there are no "clear cells," and no definite relationship of the cells to the capillaries, as usually described. The lack of uniformity in size and shape of the cells, the presence of an indefinite but demonstrable intercellular substance, and the mode of invasion of the tumor in the vicinity of the growths, aside from other histological details, seem to be diagnostic of sarcoma. If

hypernephroma exists as an entity it should have a definite and usually recognizable structure, but if it be decided that all growths arising from adrenal epithelium irrespective of histological details should be so designated, and at the same time the capability of adrenal cells to form a sarcomatous tumor be denied, the growth in question may be called a hypernephroma.

From the morphology of the cells, their fasciculated arrangement in some fields of both primary and secondary tumors, suggesting the structure of adrenal tissue, and finally from the pigmentation of the tumor cells, I have concluded that the cells of the growth developed from those of the zona reticularis of the right adrenal gland with possibly contribution from other cortical layers. That it was malignant in the ordinary sense is shown by the extensive metastasis, though local invasion in the primary situation was prevented by the resistant capsule.

The general appearance of the growth under the microscope is that of large round-celled sarcoma, with a tendency to alveolar arrangement in some fields. It unquestionably more closely resembles this class of growths than any other, and if it be desirable to give it a name, from its histological structure and from the probable histogenesis, I should call the growth a large round-celled adenoid melanotic sarcoma, believing that in the present unsettled state of our knowledge of the subject such tumors may be brought under the general class of sarcomata, however modified.

A CASE OF NARCOLEPSY, FROM A SPECIFIC INFECTION TRANSMITTED THROUGH FIVE GENERATIONS.

By Albert N. Blodgett, M.D.,
of Boston, Mass.

In a recent article, F. Raymond (*Archives Gén. de Médecine*, 1905, No. 25) alludes to the pathological varieties of sleep, especially in relation to the states of slumber which are associated with some forms of cerebral tumors; and after describing the phenomena accompanying normal slumber, he mentions a condition which would seem to represent the border-line between normal sleep and the unconsciousness often accompanying recognizable lesions of the cerebral structures. He states that mental hebetude and abnormal slumberous conditions are often observed among the first indications of serious nervous or mental impairment—that is, an increased inclination to sleep which may or may not be associated with

symptoms of disordered mental or motor activity—and varying in degree of intensity and diversity of direction, as well as in the character of its manifestation, and which may later progress to a stage of absolute coma. Among these somnolent conditions he includes narcolepsy, which was first so called by Gélineau (*Gaz. des Hôpitaux*, 1882), though the same condition had been recognized since 1861 by Casse, Marotte, Labbé, and others. Gélineau thought this disorder to depend upon a special neurosis, while Ballet believed it to be due to the action of some toxin of unknown nature within the body of the individual. This view has prevailed, with a few notable exceptions, among most of the observers who have reported such cases since the appearance of Ballet's communication.

True narcolepsy, according to Raymond, is characterized by a sudden and irresistible inclination to sleep, coming upon the individual outside the hours usually passed in slumber, and appearing with a more or less regular periodicity and with variable duration of the somnolency. He states that the person is overpowered by sleep in the midst of his ordinary occupations, and has noted the condition to arise under the most unexpected circumstances, even during meals at table. It is more frequently observed among persons who are subject to gout, rheumatism, or obesity, as well as in the course of the different autointoxications, renal, hepatic, and those due to gastrointestinal fermentations, etc. It may also accompany the different acute febrile infections. So far as I can determine from the material at my disposition, the actual specific agent of the supposed toxic action has not in any instance been detected or its nature defined.

I am able to present the notes of a case of narcolepsy in which the causative action of a specific infective agent is believed to be the source of the disorder. In this direction the heredity of the case is interesting.

The patient is a woman, about sixty-five years old, single. Her paternal grandfather was of old pilgrim stock, and was in early life strong and robust. He followed the sea, making some long voyages to the East, also to the various coasts of Europe, and during the period of the wars with England took some part in the maritime portion of that struggle. He was in the Port of St. Petersburg at the time of the disastrous retreat of Napoleon. He was married during his early manhood, at the most active period of his career. On his return from a long voyage he was found to be ill, and it is said that he had "the bad disease," for which he was under the treatment of that day for an indefinite time. Not much reliable information can be gathered upon that point at this late day, but the study of the lives of his descendants is, at the least, suggestive in diagnosis. This grandfather died in the '40s of the last century at an advanced age, leaving a large family, who

all reached maturity, with the exception of one or two who died in infancy from unknown causes. Each member of this (the second) generation bore some inherited constitutional taint, but in each member of this generation the particular form of stigma varied from that of another. The following is a brief outline of the special features in eight of these individuals whom I will designate as A, B, C, D, E, F, G, H.

A. was a daughter, who resided in a large city, and was a highly cultured and very intellectual lady; excelling especially in musical and artistic ability, and occupying an enviable position in society. Her health was always delicate, and she suffered in middle life from some affection of the eyes, of progressive nature, for which no treatment was effective, and which resulted in total blindness. The malady was not the cause of physical pain, and her health was not apparently greatly impaired, as she went about for many years and enjoyed herself in a manner which was astonishing to those who knew of her affliction. She died at an earlier age than any of her family who had survived childhood, at about forty-five years. The cause of death is not known.

B was a son who married early and had a numerous family, concerning eight members of which I have fairly accurate information. B himself was able to work at his trade during almost his entire life, but at about the age of sixty he suffered from "rheumatism," of slow and chronic character. After a few years he was the subject of a gradual decline of mental power, and at length became almost an imbecile. There were no symptoms of general paralysis of the insane.

C was a son who married early and had three children. He was, during his younger years, in good health, but at about the age of thirty-five was the subject of a "gradual contraction of the joints of the trunk and of the limbs," so that his body was greatly deformed, and he became entirely helpless; for many years was bedridden. His general health remained good, and he died at about the age of sixty. It was impossible to employ any other receptacle for his interment than a box something like a packing-case, to hold his remains. The cause of his motor infirmity is not known. His last illness was an acute pulmonary disease.

D was a son, who married early and had five children. One of these is the subject of this communication. These children all grew to maturity, and with one exception are still living. D himself was of most excellent character, industrious and sober, and for many years presented no sign of stigmata of any kind. At about middle life, however, he gradually developed chronic chorea, which persisted throughout his remaining life and much impeded his activities, until, toward the end of his life, he was unable to do any kind of labor. The chorea was especially marked in the area of distribution of the seventh cranial nerves, and resulted in ataxia,

and later in essential paralysis of all the facial muscles. The upper eyelids drooped, and he was obliged to lift the lid with his finger in order to look forward or upward. His mouth was always open, and his teeth gradually fell out until all were gone. His face hung in loose folds, and his former expression of features was lost. He could not chew his food, and when his teeth were finally lost it was frequently difficult for him to take sufficient nourishment. His speech was thick and indistinct from lack of control of the muscles concerned in speaking. Swallowing was difficult on account of ataxia of the pharyngeal apparatus, and he often choked while eating and always in drinking. Visual and auditory functions were normal. The head was continually carried far forward from weakness of the nuchal muscles, and the back of the neck was disproportionately long. The muscles of the trunk were less affected; the arms were only partially under voluntary control. The patient always shaved himself, though to the onlooker it seemed as if he must cut his throat at each motion. The legs were fairly strong, and he could walk considerable distances without fatigue. The gait was alcoholic rather than ataxic. His bodily condition did not materially change during many years, though his mental powers became weakened with advancing age, and he became peevish and irritable to a marked degree, though not actually demented. Coincident with the mental changes was a gradual progressive emaciation in flesh; what his condition might have become, had he lived to a more advanced age, it is of course impossible to say. He died at the age of seventy-six of some pulmonary affection after a short illness. There is no history of endocarditis or of acute rheumatism in his case. The course of the choreic infirmity in this patient somewhat resembles that described by Osler ("Remarks on the Varieties of Chronic Chorea and a Report upon Two Families of the Hereditary Form, with One Autopsy," *Journal of Nervous and Mental Disease*, February, 1893), in which he reports several cases of this disease. The patient whose choreic infirmity is incidentally described in the present communication does not, however, afford an example of the progressive nature of the malady, as pictured by Professor Osler; and his condition did not apparently suffer any noticeable change for many years. His decline in physical and mental vigor may reasonably be ascribed to senile changes which might be expected to appear at an even earlier stage in a patient so long affected with a serious disorder of the important co-ordinative nervous centres.

The pathology of chorea is not clear, and not much apparent gain has been made in reference to its causation or seat or the nature of its anatomical lesions, if any. The theory of a toxic origin has not been proved. Heredity, or at least transmissibility, seems more probable, and that the inherited taint is not necessarily essentially choreic in character in the ancestor. Chorea is not

infrequently observed after the acute febrile infections, but is then usually of only transitory duration, and not chronic or progressive in character. If endocardial complications exist the course and progress of the disease may be dependent upon the nature and seat of the endocardial damage, and may or may not be of serious importance to the well-being of the patient in the future.

E was a daughter, and was well until about eighteen, when "some bone disease" developed, which was followed by deformity of the trunk (probably some carious affection of the spine). This healed after a time, and this person married and had three children, who were apparently normally developed, and seemed to be free from inherited taint. One of them, however, at about the age of eighteen, became the subject of obscure cerebral symptoms, which were followed by gradual impairment of the mental faculties, and led to a practically idiotic condition, and she died at about the age of thirty, almost an imbecile.

F was a son, who left home at about twenty and was never heard from later.

G was a daughter, who "was always very nervous," but did not develop special symptoms, so far as is known in the relationship. She died at an advanced age.

H was a daughter who was also "very nervous," but who developed no stigmata.

Of the second generation five members are known to have had offspring, numbering from one to eight. A short resume of these persons is appended.

A was blind and died in middle life without issue.

B had eight children, all of whom were strong and well until maturity, when several of them began to exhibit symptoms of the inherited stigma of disease. Five individuals of this family suffered from gradual impairment of vision, due to optic atrophy, which went on to total blindness in four, and in a fifth, sight was reduced to perception of light. One member was afflicted with some affection of the hip, which lasted for some years, and resulted in impairment of the joint and about two inches of shortening of the limb. Another suffered from mental trouble of melancholic type, and was under asylum care for a considerable time. She resided in a remote part of the country, and nearer information of her condition is lacking. All the female members of this family are neurasthenic, hysterical, and subject to constant fear of impending evil, which would seem to be grounded upon a justifiable state of reasonable apprehension of hereditary disease. Several of those who became blind have showed extension of the optic degeneration to the cerebral structures, with subsequent symptoms of softening, going on to slow impairment of the mental powers. None has presented signs of any acute meningeal complications.

C had three children, of whom one was dissolute and improvident,

and was considered weakminded. He died in middle life from some unknown cause. One of the others was the subject of "hip and spinal disease," was seriously deformed, weak mentally, and died in middle life, the cause of death given by the family being that "she went into a decline." The remaining member of this family was weakminded, hysterical, vain, improvident, and unreliable; she died from some unknown cause in middle life. Thus there was no surviving issue.

D had five children. All of these were of decidedly "nervous" temperament and occasionally exhibited indications of motor incoordination, suggestive of the choreic affection from which D (the father) suffered, but no member of this generation has developed the condition to an appreciable degree.

In the fourth generation from the original ancestor in this family, there have been about twenty members. Of these, about fifteen are believed to be living. Three infants of this line died from some affection attended with convulsions, and another became dissipated and a vagabond, and is believed to be dead.

The remaining members, so far as known, are all of "nervous" temperament, but have not as yet developed any special tendencies toward any of the affections from which the former generations have suffered. It would seem that the original taint has become attenuated by successive dilution with healthier stock, until the original infective element has become practically extinct. There has been one infantile death in the fifth generation from convulsions, but the circumstances attending this case are not definitely described.

The patient who forms the real subject of this communication is of the third generation, a lady now about sixty-five years of age. She was well as a child, and left home at about eighteen, to engage in mercantile occupations, and has remained in the same employment and position ever since that time. She has resided with the family during all these years, and though depleted by the death of nearly all its members, she and her employer have remained together. These two now constitute the entire household.

The patient began to notice her infirmity at about twenty-two years, when the attacks are described as suddenly appearing in the form of an irresistible inclination to fall asleep. She became subject to somnolence at all times of the day, without known cause or apparent provocation by surrounding circumstances. Otherwise she seemed to be in her usual health. One attack afforded no protection from a recurrence of the same character, and she has been known to have a succession of them during the whole of an entire day. She seems to fall into a perfectly natural slumber, and can easily be roused by a call or by any unusual noise. She wakens readily, and is apparently unaware that she has fallen asleep. At other times the sleep is more profound, and she realizes that she has passed an appreciable interval in unconsciousness. She is

never confused, or in any other way noticeable after the attack, and sleeps regularly at night, as other persons are accustomed to do. During a period of more than forty years the lady has suffered from this condition, without appreciable change in the character of the manifestations of the malady, though careful observers think that within ten years there has been a noticeable deterioration in her general mental condition; that she seems somewhat dull and has not her usual acute perception in matters in which she was formerly very accurate. It is now believed that she is suffering from diabetes, but of this I have no personal proof. Otherwise she seems as well as could be expected in a lady of her years; considering that she has constantly worked very hard at a taxing occupation, and has lost little time from illness, nor has she been accustomed to take time for relaxation or recreation. The attacks are now in no appreciable way different from those at first observed; and the mental decline may perhaps be due only to the approach of old age. Her figure is full and rather plump, her color is good considering her age, but is somewhat ashy in hue. Her appetite is good, her strength remains fairly good, but she feels "that she is not so strong as she was." For a time she "dieted," but now she "eats all she wants" without harm. She states that she has had a series of "diabetic ulcers" within the last few months, which have healed under mild treatment. Her sight has also become very weak, so that she can read only the largest print. This may be the result of long abuse of her eyes, or it may be simply another accompaniment of her age. There has been no pain or other acute symptom in her failing vision, and it may be connected with the diabetic (?) process. There is no history of acute rheumatism or endocarditis, nor of any other infective or constitutional disease. The thyroid is neither hypertrophied nor absent.[1]

Almost nothing is known of the pathology of narcolepsy. The description of its causes, written by Aretæus, comprises nearly all that we know at present.[2] He states: "Multus somnus refrigerat et resolvit et stupefacit." And further on: "Somnus multus crassitudinem corporis et ignavium facit, et nebulam quandam sensibus offendit; medoicris autem prodest." (Aretæus Cappadocis, Causis et Signis Morborum. Johannes Wigan Oxaniæ: MDCCXXIII.) (See Latin translation.) Andreus Pizlerus, writing almost fifteen hundred years later, states essentially the same thing in the following: "Præsumptio ergo, spiritus in organa sensum minus influere, sed poris cerebri obstructis vel obrui, vel impediri quo minus commercium cum objectis extrinsesis exerceri et conceptus

[1] Since the above was written, the urine of this patient has been examined by an authority whom I respect, with the following result: Color, light amber; reaction, strongly acid; specific gravity, 1012; sediment, very slight; albumin, very large trace, by three tests; reaction for sugar (glucose) gave absolute negative result. A confirmatory examination of the urine by another authority gave the same qualitative results.

[2] The contemporary of Galen, born A.D. 131, died near the end of that century.

ideales ut prius formari possint." (*Dissertatio Medica de Affectionibus Soporosis et Catelepsi*, a Andrea Pizlero, Jenae, MDCCVIII.) He also quotes Horace (Satirum sive Sermonum, Lib. iii, v. 145 et seq.): "Quondam lethargo grandi est oppressus," etc.

Porter states that "it is not the length, but the character of the sleep and the associated symptoms that make narcolepsy a distinct disease."

Putzel, in a recent work on *Functional Nervous Diseases*, classes narcolepsy under the heading of "epileptoid sleep states," and remarks that " it is very probable that narcolepsy will find its appropriate place among the minor epilepsies, and occupy the borderland between the epileptic and the non-epileptic conditions." . . . "The narcolepsies in a general way are recognized not from their character, which is that of true sleep, but from the frequency of the attacks, suddenness of onset, and their irresistible nature."

Finally, a pathological form of sleep, or at least a slumberous condition, may be produced by some affections, or probably rather, infections, accompanied by recognizable lesions of the nervous system. Among other possible causes, it is now generally accepted that the invasion of the body by the parasite of trypanosomiasis is the potent causative agent of the series of progressive symptoms, which uniformly persist and usually lead to the development of that inevitably fatal disease, called for want of a better name, the "sleeping sickness."

The theory that narcolepsy is caused by some toxic action within the system, either of autogenous or extraneous origin, seems to be supported to some extent by the rather frequent reported association of the narcoleptic condition with diabetes or obesity, which latter are usually only observed at a much later period than the morbid inclination to sleep. It may be that its association with these two conditions is only accidental, or that the same causative action (possibly of metabolic character, or related to some chronic nervous impairment), may produce both the narcolepsy and later the symptoms of diabetes or of obesity. This would correspond with the known production of diabetes experimentally by traumatic injury of certain parts of the central nervous system. No definite information upon this correlation of symptoms in narcolepsy is yet available. The pathology of the affection is still shrouded in obscurity.

The treatment of the nervous phenomena has been much simplified since we have realized that nothing is definitely known of the causation of the symptoms. In the thesis of Pizler, to which reference has been made above, the treatment advised was sufficiently active if not efficient. He recommends cupping, leeches, venesection, irritant clysters, emetics, purgatives, even the moxa, with irritative applications to the hands, feet, and body, etc.

The modern conception of narcolepsy has gradually resulted in the abandonment of most of the remedial treatment formerly

employed, until at present it consists almost entirely only of measures adapted to the hygenic and moral condition of the patient. If diabetic symptoms are detected they may be ameliorated by suitable diet and other treatment as indicated, and in some cases favorable results seem to have followed their exhibition; but no treatment thus far advised has seemed to effect any appreciable result (with one or two reported exceptions) in the direction of relieving the somnolency or in restoring the patient to a normal condition.

If this case be accepted as one of so-called "narcolepsy" (which, after all, is only one of the prominent symptoms of the disorder), as described by the authorities quoted above (and to my mind there can be no hesitation in so considering it), this affords some support to the theory of the "toxic" or "hereditary" or "transmissible" character of this obscure condition. The facts which would seem to support this theory date back to the third generation, antecedent to this patient, to a direct ancestor who was afflicted (according to the belief of trustworthy relatives) with an acquired infection of specific character which is known to be transmissible to posterity. The direct progeny of this ancestor, so far as known, all suffered from stigmata referable to direct inheritance, but not in the same way as that in which the original patient was affected. In all the direct offspring the disease appeared in the form of affections of the nervous system, with a strong predilection for the special senses. Some of the members of this generation suffered from degenerative changes in the special nerves of sight; some with troubles of irritative or cortical character; and some with affections of the co-ordinative or convulsive centres or distributions.

The results in the third generation are most appalling. Here were four members of one family stricken with blindness; four others were affected with organic or functional diseases of varying character, all referable to instability of the nervous system, and all tending to progressive degradation of the higher cerebral functions. In another line of the direct offspring the taint is observed in a convulsive form, impairing the motor functions, with terminal degeneration of the higher nerve centres. In still another the form is of a spastic character, lasting many years, but progressing to a final decay of the central intellectual functions. In short, each member of this unfortunate generation bore an inheritance of disease and death.

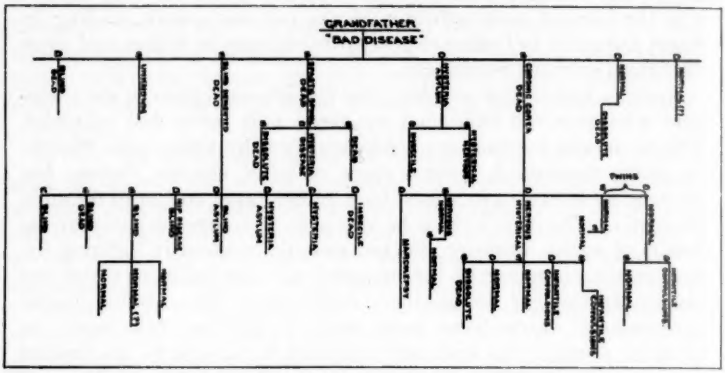
The condition called "narcolepsy" appeared in a member of the third generation, whose father was affected with chronic chorea. In another descendant of this father is found a series of deaths from infantile convulsions, and this tendency is transmitted in this line to the fifth generation from the original ancestor. Such an array of facts seems much more than a mere simple coincidence; and it appears rational to believe that this appalling history is a record

of the results of one original acquired constitutional infection, appearing in a rather long line of cases, illustrating the varying forms which it may take. But the most striking fact is this, that in each member of this considerable number of individuals the transmission is in the form of some affection of the nervous system, leading by direct extension to further degenerative changes in higher and more important nervous machinery.

Another fact is also striking: that the inherited taint in the members who survived childhood appeared only after full maturity. This is noticed in relation to chronic chorea by Osler, who reports, as above mentioned, several cases of adult chronic chorea; but most of these cases progressed by a rather rapid course to terminal dementia. On one of these he was able to secure an autopsy, the results of which, however, did not essentially assist in defining the seat or the character of the supposed nervous lesion to which the disease is thought to be due. Aside from the careful clinical observations which have been made in the last few years no essential progress has been accomplished in relation to this obscure disease. Of its "Wesen" we are as ignorant as ever. It is not more remarkable that from the choreic father a daughter should develop narcolepsy than that her father should have developed chorea from an inherited constitutional taint which was not similar in his own father.

The pathology of narcolepsy is rendered more obscure, and the seat of the lesion to which it is supposedly due is more difficult to determine, from the fact that the disease is not often fatal, the death of those affected with it being more generally long delayed and due often to other and independent causes, such as diabetes or its consequences. In most of the cases reported the patients have either been lost sight of or have lived many years, finally succumbing to maladies unconnected with the nervous disorder. In chronic chorea, when the disease follows the course depicted by Osler, and the case progresses to terminal dementia, with the practical obliterations of all the mental faculties and functions, there may well occur a variety of histological changes in the more important higher centres which would be misleading. In the case of chronic chorea included incidentally in this communication the motor symptoms were for many years practically stationary in their manifestations, and the gradual deterioration of physical and mental vigor in the patient may reasonably be assigned rather to advancing senility than to the choreic degeneration with imbecility, described by Professor Osler. The patient died at a greater age than most individuals attain, and except for the infirmities connected with his disability and the difficulties sustained in his nutrition, owing to impaired deglutition for many years, he was as comfortable as most old people until nearly the end of his life. Unfortunately no autopsy could be obtained.

A family chart is appended, showing the distribution of the inherited constitutional infection in the line of offspring to the fifth generation.



Many of the references quoted in the "bibliography" attached have been consulted in their original form, and an effort has been made to confine the list to the subject of "narcolepsy" as closely as possible.

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AN UNUSUAL CASE OF ANTITOXIN RASH.

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The patient, who was the subject of the condition described in this note, is an American woman about thirty-five years of age, whose maternal grandmother was of Spanish blood. During childhood she was an asthmatic, and since reaching maturity she often has had attacks of hay fever. She also gives a history of occasional urticarias following the ingestion of strawberries or shellfish.

Because of the illness of her daughter with diphtheria, she was given by me, at her home in the country, a prophylactic injection of a thousand units of antitoxin. There was no nervous shock from the injection, the patient walking immediately afterward into another room. In about four minutes she called me, complaining that she did not know what was the matter with her head and face —the head felt so full and the face so flushed. Following this in rapid succession came total hyperæmia of the skin, with terrific itching and the development of immense white weals. Then the lips, tongue, and eyelids began to swell and the patient complained bitterly that she could not breathe, that she was going to die, that her heart was thumping against her chest so hard that it pained her. The pulse, which was at first very rapid, soon became imperceptible at the wrist, although the apex-beat was very vigorous. It was only by much encouragement and great will-power and the use of stimulants that consciousness was retained. The heart-beats soon became irregular and less vigorous, the pulse weak and thready, or imperceptible, and the face now became a peculiar ashen gray. The color faded from the neck and chest, but the limbs and abdomen were still intensely hyperæmic and covered with weals, and itched intensely. Following the first period of partial collapse a typical severe asthmatic attack came on which produced still greater difficulty in breathing and was accompanied by the usual sounds in the chest. This lasted for a short time, the pulse improving meanwhile, but was succeeded by a second sudden flushing of the face followed again by the peculiar ashen appearance of the face, and disappearance of the radial pulse. The patient retained consciousness, but felt sure that she was dying. She maintained control over herself admirably and fought against the sensation of impending death. With the administration of hot black coffee the heart action improved and she felt temporarily better. She then began to complain again of the tongue and lips swelling and felt as if she could not draw air through the larynx. Air was drawn into the chest with great difficulty, but the signs of asthma were absent, and the

whistling sounds accompanying respiration seemed to come entirely from the larynx. An œdema of the larynx was diagnosed. For a time the condition grew steadily worse, the patient became cyanosed, the breathing very labored, and the laryngeal sound loud and terrifying. When a hurried tracheotomy seemed inevitable she began gradually to improve and her respiratory and cardiac symptoms largely disappeared. The rash came out on the face again, and within one hour after the injection she was able to be moved to her room and put to bed. During the attack she had been unable to lie down and had to be held in a sitting position before an open window. For the next thirty-six hours the patient was in great anguish from the intense itching and burning of the skin over the whole body. The pulse remained about one hundred to the minute, but there was no rise of temperature. The rash then rapidly subsided, and except for a few scattered weals and some joint stiffness she soon regained her normal condition of health.

In considering the case it is interesting to note that her sister, who was given a similar injection later in the same evening of the same kind of antitoxin, had no rash for six days, and then a rather severe one lasting for thirty-six hours and followed by some joint-pains. Her four-year-old niece, a child of her brother's, had irregularity of heart action and drowsiness following the injection, but only a moderate rash six days later. Her daughter, the diphtheria patient, received fourteen thousand units in all and had no disturbance from the antitoxin until eight days after the last injection, and then a rather severe scarlatinal-like eruption accompanied by a low fever, of two days' duration, then a two days' lull and a second eruption, with temperature up to 102° and a high heart rate. It is of importance to note that all of these patients had a certain percentage of Spanish blood in their veins, and that they all had some form of rash, although a number of other relatives by marriage and exposed children had injections at the same time, and none of them developed rashes.

The striking feature of the case is the sudden onset and the severity of the symptoms. The circulatory disturbances seemed to be due to a sudden intense vasomotor dilatation in the skin and mucous membranes, with the inability, for the time being, of the heart to receive enough blood for circulation, hence its rapid, forcible, inefficient beating. Its suddenness leads one to suppose that the effect of the injected element causing the rash may have been upon the central nervous system—the vasomotor centres—producing, perhaps, a peripheral vasomotor paralysis. The mucous membranes seemed to be similarly affected and to undergo a certain amount of temporary œdema. Probably to this was due the asthmatic symptoms. There is no history of angioneurotic œdema or of œdema following bee-stings or insect-bites given by the patient.

Two weeks previously the patient had ether administered for

tonsillectomy; a hypodermic injection of morphine and atropine given at that time raised a weal at the site of injection. Whether any after-effects of ether on the liver or nervous system played a part in this peculiar action of the antitoxin is a question.

The emergency treatment used was that at hand. She was given immediately strychnine sulphate 1/20 grain by the mouth. This was followed by numerous small cups of hot black coffee, given at frequent intervals. Six drachms of Epsom salts in hot water was given early and a high large soap-suds enema was given and repeated shortly after. One and a half hours after administration of the antitoxin vomiting occurred, with considerable relief. Within two or three hours the bowels were acting vigorously. Alkaline sponge baths were given constantly, and milk of magnesia, a tablespoonful every three hours, was administered internally. Locally, some relief was obtained from a 5 per cent. solution of carbolic acid in milk of magnesia. The next two days sodium carbonate tub-baths temporarily relieved the intense itching. The most relief was obtained from the use of a spray consisting of: menthol 2 drachms, and ether, chloroform, and spirit of camphor each 6 drachms; followed by the use of a powder consisting of: powdered camphor 1 drachm, powdered zinc oxide 3 drachms, and powdered starch 1 ounce. The second day following the injection was made tolerable by the use of veronal and heroin as sedatives and by the administration of one teaspoonful every four hours of the following mixture: magnesium sulphate and calcium chloride each 4 drachms, chloroform-water 1 ounce, tincture of orange-peel 1 ounce, distilled water sufficient to make 3 ounces. On the third day, except for swollen eyelids, coated tongue, anorexia, joint pains, and some rash, the patient was practically over the experience. She has since been quite well.

REVIEWS.

A Treatise on Diagnostic Methods of Examination. By Herman Sahli, Director of the Medical Clinic, University of Bern. Edited, with additions, by Francis P. Kinnicutt, M.D., Professor of Clinical Medicine, Columbia University, and Nathaniel Bowditch Potter, M.D., Visiting Physician to the City Hospital, New York. Authorized translation from the fourth revised and enlarged German edition. Philadelphia and London: W. B. Saunders & Co., 1905.

Perhaps the most complete and exhaustive work on diagnosis and diagnostic means is the American translation of this great teacher's work. Probably no American or English work on this subject is so up-to-date and accurately descriptive, and certainly no similar book anywhere can claim, as does Sahli's, that it is the result of years of one man's observations and adaptations and not, like our standard diagnostic works, a mere compilation.

History taking and general considerations derived from first impressions of the patient form the opening chapter. The more striking local manifestations of many diseases are here considered, as, for instance, œdema of the skin, its theory of causation, collateral circulation, the striking exanthemata (an excellent picture of the typhoid roseola).

A fuller reference to the obscure fevers would have improved the notes on temperature, while eleven types of dyspnœa suggest a refinement in differentiation not often met.

Pulse and blood pressure, the next subjects considered, can scarcely be excelled in description. The latter is taken up technically and practically. The former includes a discourse on venous pulsation, which will make clear this difficult corner in diagnosis to any who will read.

The explanation of the phenomena of percussion, the theory and practice thereof, far exceeds one's expectations, and has been made by historical references an attractive section, and the scheme and description of the pleuropericardial rub is novel and interesting. The condition of heart-block is given consideration and valvular heart lesions are lucidly explained. Why abdominal inspection should be inserted in the middle of the heart's description is not evident.

As might be expected it is the section on diagnosis of gastric disorders that is most eagerly sought, and no disappointment is experienced. Fuller by far than any other work, with chemistry for the chemist, practical points for the practical, it gives one a new conception of investigation and diagnosis of gastric functions. Particularly interesting is the new butyrometric test for absorption.

The examination of the rectum is given in a special place, but it appears incomplete without mention of the conditions found by rectal examination in appendicitis.

Very practical is the consideration of the gross appearance of the feces; very careful the description of quantitative estimations of waste products and undigested or unabsorbed food matters. The intestinal parasites are fully reviewed, the new world hookworm being given mention.

We can recommend the chapter on examination of the urine to any student's or worker's investigation; especially fine is the discussion upon nucleoalbumins, serum albumins, albumose (an excellent table of differentiating reactions of albumins and albumoses is appended). A table of reducing substances present in the urine adds to the pages on glycosuria. Cryoscopy, electrical conductivity are described, and the chemistry of total nitrogen and the waste products, so much studied at present, is carefully gone into.

Sputum and clinical bacteriology are serviceably considered. The plates are not particularly good or instructive.

We cannot be enthusiastic about that part of the book given over to the blood and its diseases. The plates are poor and wrongly lettered. Undue credit is given Koch with regard to malaria. Trypanosomiasis is not mentioned.

Special chapters on the mouth and tongue, with good plates and a first-rate resume of the results of cytodiagnosis, are among the additions by the American authors; the *x*-ray chapter is their work as well.

The nervous system required two hundred pages for its investigation, and is complete to a degree. Many new schemes and diagrams are introduced. One should particularly mention those describing the reflexes and the systems controlling the bladder and rectum. Most of the pictures seem to be from the American clinics.

An addendum to general diagnosis, including further work on the pulse tracings, etc., follows the chapters on the nervous system, and concludes the book.

With regard to the arrangement of the book one can say that perhaps the somewhat indiscriminate grouping observed is rather confusing when searching for a particular subject. Bacteriology, for instance, suffers by being appended here and there in different sections.

N. B. G.

A TEXT-BOOK OF PHARMACOLOGY AND THERAPEUTICS, OR THE ACTION OF DRUGS IN HEALTH AND DISEASE. By A. R. CUSHNY, M.D., Professor of Pharmacology, University College, London. Fourth edition. Philadelphia and New York: Lea Brothers & Co., 1906.

THE need for a new edition of this work having arisen through the appearance of the eighth decennial issue of the United States Pharmacopœia, the author seized the opportunity to include in the new edition the advances made in pharmacology during the last few years. Those who are already familiar with the quality of Dr. Cushny's work will welcome the new edition without any special introduction. The changes that have been made do not affect the general plan of the book, and the classification of drugs adopted in previous editions has been retained. Considering the long list of new drugs that claim the attention of systematic writers every year, it is remarkable that the author has succeeded in keeping this volume within reasonable dimensions without omitting to mention the most important additions to the Pharmacopœia. The discussion of purely pharmacological questions, with few exceptions, deals with the information gained through experimentation rather than with the experiments themselves and with conflicting theories; this avoidance of lengthy and tedious reports of experiments keeps the book within the scope of students and practical doctors. The opinions advocated on questions that are still under discussion do not call for special remark, and it does not appear that the last few years have been productive of any important final decisions on moot points, such as the food value of alcohol and the like. One might wish that the author had been a little more emphatic on the subject of antipyretics and the dangers attending their use; for it is unfortunately a fact that many practitioners still fail to realize the dangers which have recently given rise to so much agitation both in the medical and in the lay press. It is true that the practice of prescribing coal-tar derivatives in the treatment of fevers is "deprecated," and a general warning is uttered as to their dangers in neuralgia and headache; but one seems to read between the lines that the present agitation in the author's opinion is somewhat overdone. Brief consideration is given in Part V to ferments, secretions, and toxalbumins. The ferments are disposed of in a very few pages, which are chiefly devoted to their physiological aspect, as the author is evidently convinced of their absolute uselessness in practical medicine. Under the head of internal secretions thyroid gland extract, or rather iodothyrin, receives full consideration. Other internal secretions, such as extracts of the pituitary, the thymus gland, etc., are dismissed with a few words. Suprarenal gland preparations are discussed under the head of circulatory stimulants.

On the whole the pharmacological part of the book completely overshadows the therapeutic portion, which is limited to a bald statement of the various preparations of drugs and a few general indications for their use. Administration is not discussed at all, and there is nothing to tell the reader which preparation he ought to select in a given case. The difficulty is very often not what drug to use, but in what form, in how large a dose, and at what intervals. These subjects are only treated in the most general way in the introduction or in occasional passages hidden away in the text.

Each article is provided with a bibliography which the student will find exceedingly helpful. The book is also supplied with a list of drugs classified according to their therapeutic use and a very good index. R. M. G.

A TREATISE ON THE NERVOUS DISEASES OF CHILDREN. FOR PHYSICIANS AND STUDENTS. By B. SACHS, M.D., Alienist and Neurologist to Bellevue Hospital; Neurologist to the Mt. Sinai Hospital; Consulting Physician to Manhattan State Hospital, New York. Second edition, revised. New York: William Wood & Co., 1905.

THE first edition of Dr. Sach's well-known treatise was so carefully written and covered the subject so completely that little opportunity was left for improvement after the ten years that have elapsed since the book was given to the profession. The most noticeable change has been the condensation of the text from 656 to 557 pages. This has been accomplished by omitting the bibliography at the end of each chapter and by omitting the chapters on the anatomy, physiology, and pathology of the spinal cord, on the anatomy and physiology of the brain, and on anæmia and hyperæmia of the spinal cord, and the appendix on therapeutic suggestions.

The consideration of anæmia and hyperæmia of the spinal cord has long appeared in formal text-books on neurology, with more or less open apology for their inclusion as distinct diseases. It is therefore a step in advance that Dr. Sachs has at last refused to follow the custom which is continued in later text-books simply because the older writers labored to describe definite symptoms due to varying states of the blood supply of the spinal cord. With the exception of the direct effects of concussion upon the cord and its membranes, which are usually discussed under this special heading, the condition of anæmia and hyperæmia is best considered in association with other morbid states and more important clinical

symptoms, as Sachs pointed out in his chapter on the subject in the first edition of his work.

The reasons for the omission of the valuable chapters on anatomy and physiology are less obvious; and as the original volume was not overcrowded, it seems to us a mistake to have sacrificed them simply for the sake of condensation, and because, as the author states in his preface, the subject matter can be found in other text-books.

The additions are not numerous—a few lines here and there ingeniously fitted into the original plates, some larger additions at the end of each chapter, a few new illustrations, and a section on amaurotic family idiocy, which was not discussed in the first edition. In saying this, however, we in nowise wish to detract from the value of the second edition. It simply serves to emphasize the fact that the author found little to improve or change in an already nearly perfect work, which has been honored by translation into German, Italian, and French, and will continue for a long time to come to be quoted as the standard text-book upon this important and little specialized division of pediatric medicine.

T. S. W.

THE PRACTICE OF MEDICINE. A TEXT-BOOK FOR PRACTITIONERS AND STUDENTS, WITH SPECIAL REFERENCE TO DIAGNOSIS AND TREATMENT. By JAMES TYSON, M.D., Professor of Medicine in the University of Pennsylvania and Physician to the Hospital of the University; Physician to the Pennsylvania Hospital; Fellow of the College of Physicians of Philadelphia; Member of the Association of American Physicians, etc. Philadelphia: P. Blakiston's Son & Co., 1906.

THE fact that the fourth edition of this book has appeared only two years after the third edition indicates that its merits have been recognized by the profession. The main change in this edition has been in the rewriting of the section on animal parasites by Prof. Allen J. Smith, who is recognized as an authority on this subject. The section has been improved by the addition of a number of illustrations, and the contents are of such a nature that a comprehensive knowledge may be obtained of animal parasites not only from a medical but also from a biological point of view.

One of the most pleasing features of the work is to be found in the historical sketches of a number of the diseases; this adds considerably to the interest of the reader. Another commendable point is the use of italics in emphasizing important or distinctive features, or especially reliable methods of treatment. This should

aid the student materially in grasping the essentials from among the mass of details which must of necessity be included. The discussion of each phase of each subject is sufficiently full; and being interspersed with the opinions and reports of various authorities and investigators, the matter presented is complete. The personal views and experiences of the author are frequently and fully given, and in the case of Prof. Tyson are of decided weight; as his opportunities for the clinical study of disease have been exceptional, and his painstaking, careful methods make his observations of distinct value. Numerous references are given in footnotes, so that the original publications from which facts have been extracted may be consulted.

Still another particular that makes this volume of more value and adds to its convenience is the fact that there are included in it descriptions of the technique of the more commonly used methods of clinical diagnosis. There are instructions in the methods of examining sputum for the tubercle bacillus, for staining blood, and for examining blood for the plasmodium of malaria. There are also descriptions of the tests for determining the character of the gastric juice and the urine.

While some of the most recently advanced theories regarding the nature and treatment of certain forms of disease have been omitted it may have been decided by the author that these are supported as yet by too little proof.

The book contains a good index, and is on the whole one that will be found complete and satisfactory as a book of reference, and excellent as a text-book. F. W. S.

COUNSELS AND IDEALS FROM WRITINGS OF WILLIAM OSLER, M.D. Boston and New York: Houghton, Mifflin & Co., 1905.

DR. CAMAC, with what might be termed an excess of modesty, has refrained from placing his name upon the title page of this most admirable little collection of wise laws and modern instances, drawn from the writings of the man who holds the most commanding position in the English speaking medical profession at the present time. We may be allowed however, to congratulate the compiler on the great skill which he has manifested in the selections which he has chosen, and in his arrangement of them. Dr. Osler has written and spoken on most of the subjects with which the life of the medical man is brought in touch, and we may be sure that everything that he has let fall possesses a peculiar value. It is only necessary to glance at the titles of the forty-seven

articles from which this book has been derived to see what a wide field Dr. Osler has covered, and to what varied audiences he has spoken. The book is a collection of good things, and it is, therefore, impossible to single out individual portions of it for special mention. There are twenty sections, and the topics dealt with comprehend the entire philosophy of life. It is sincerely to be hoped that the work will obtain a wide circle of readers without the pale of the medical profession. Dr. Osler is much more than a physician, he is a philosopher, and a practical man of affairs, and there are few who could not read this book and derive from it lessons which would be of benefit to them in their daily life. Most physicians have already read its contents, as they have appeared in current medical literature, and no doubt many have wished that they could be put in just some such permanent form as has been done by Dr. Camac. To him we feel, therefore, under a special debt of gratitude. F. R. P.

Les Taches de Koplik; Leur Importance pour le Diagnostique et la Prophylaxie de la Rougeole. Par André Bing, Docteur en Médecine, Licencié es Sciences. Paris: G. Jacques, editeur, 1905. New York: Paul B. Hoeber.

The recognition of the value of Koplik's spots as a pathognomonic early symptom of measles has become so universal in America that the appearance of the present monograph at first sight seems a trifle behind time; but even a cursory perusal of its pages suffices to convince one that the author has presented for his own countrymen an exhaustive study of the subject and has discussed the essential characteristics of this sign so lucidly that every French physician into whose hands this monograph may fall can have no just excuse for confusing this lesion with other morbid appearances of the oral mucous membrane.

Such a study by a French writer is all the more of value since little attention seems to have been given to the subject in France, and the few French authors who have referred to it at all, among whom are Gillet, Guinon, Marévéry, Renault, Serinelli, and Roger, speak of the bluish-white point as being from 2 to 6 mm. in diameter, when in reality it is only a few tenths of a millimetre. The claims of priority made by friends of Flindt, Filatow, and Bielski are convincingly refuted, and the honor of the discovery and adequate appreciation of the value of this sign is justly conceded to Dr. Koplik.

The present monograph, which covers fully 194 octavo pages, including a bibliography of 234 references, must be accepted as a complete exposition of all that can be written up to the present about this interesting sign, and constitutes a deserved memorial to the fame of its discoverer. F. S. W.

THE PATHOLOGY OF THE EYE. By J. HERBERT PARSONS, B.S. D.Sc. (LOND.), F.R.C.S. (ENG.), Assistant Ophthalmic Surgeon, University College Hospital; Assistant Surgeon, Royal London (Moorfields) Ophthalmic Hospital; Ophthalmic Surgeon, Hospital for Sick Children, Great Ormond Street. Vol. II. Histology. Part II. New York: G. P. Putnam's Sons. London: Hodder & Stoughton, 1905.

THE second volume of Parsons' *Pathology of the Eye* completes the subject begun in the first, taking up in succession the lens, vitreous, choroid, retina, optic nerve, orbit, and lacrymal apparatus. It exhibits the same excellent characteristics as the preceding volume. Like it, it is exhaustive in its consideration in turn of the various disease forms to which the ocular structures are subject. A bibliography of the most important contributions is appended to each subject.

It will no doubt remain for many years the standard work upon the subject with which it deals. It is difficult to see how it can be replaced until the whole subject of ocular pathology will have to be rewritten as the standpoint changes from which the science is reviewed. T. B. S.

THE CHANGES PRODUCED BY INFLAMMATION IN THE CONJUNCTIVA (HUNTERIAN LECTURES, ROYAL COLLEGE OF SURGEONS, 1905). By M. S. MAYOU, F.R.C.S., Jacksonian Prizeman and Hunterian Professor, Royal College of Surgeons, Eng.; Ophthalmic Surgeon to the Hospital for Paralysis and Epilepsy, Maida Vale. London: John Bale, Sons & Danielsson, Limited, 1905.

THIS excellent monograph belongs to a class of books which are only too few, for it is not simply a compilation but gives the fruitful results of original research. It contains part of the book which obtained the Jacksonian prize in 1903. That part of the book which is most original relates to studies upon the microscopic structures of the normal and the diseased conjunctiva and the effect of the *x*-rays upon it. The clinical descriptions of the diseases are of course common property, which is also true of most methods of treatment, etc.

In connection with trachoma, the author details his experience with the *x*-ray treatment, which method he was the first to introduce, finding no serious effect upon the globe or other structures under *x*-ray treatment of rodent ulcer and lupus of the eyelid The granules disappear very rapidly under *x*-rays; the same result

can be attained by operative methods which have the additional advantage of removing the diseased tissue, but many patients are averse to undergoing any operation. No mask is necessary; the upper lid is everted and the lower lid pushed up so as to cover as much of the cornea as possible, but in severe cases of pannus the cornea is left exposed. A few weeks of treatment cause the granules to disappear, leaving a supple, non-contracted, non-scarred conjunctiva—certainly a great improvement over the cicatrices produced by other methods.

Pannus, especially if recent, often clears with great rapidity, the patient noticing improvement from almost the first exposure; but even dense opacity will often clear considerably. Recent cases, subacute and chronic, naturally yield the best results.

The author sums up the chief advantages and disadvantages of this treatment as follows: (1) Considerably less deformity of the lid after treatment. (2) Painlessness. (3) Pannus clears more thoroughly. The chief disadvantages are: (1) All patients do not react well to *x*-rays. (2) Difficulty of deciding when to cease treatment.

In the periods of rest between the exposures to the *x*-rays the application of copper is very useful, but care must be used as the reaction produced by it is intensified by the previous application of the *x*-rays. T. B. S.

PROGRESSIVE MEDICINE. A Quarterly Digest of Advances, Discoveries, and Improvements in the Medical and Surgical Sciences. Edited by H. A. HARE, M.D., Professor of Therapeutics and Materia Medica in the Jefferson Medical College of Philadelphia, etc. Assisted by H. R. M. LANDIS, M.D. Vol. I., March, 1906 Pp. 304. Philadelphia: Lea Brothers & Co.

THE subjects considered in this volume are: (1) The Surgery of the Head, Neck, and Thorax, by Charles H. Frazier, M.D. (2) Infectious Diseases, including Acute Rheumatism, Croupous Pneumonia, and Influenza, by Robert B. Preble, M.D. (3) The Diseases of Children, by Floyd M. Crandall, M.D. (4) Rhinology and Laryngology, by D. Braden Kyle, M.D. (5) Otology, by B. Alexander Randall, M.D.

These subjects seem to be adequately covered, the various papers reviewed being interpolated by critical remarks by the reviewers. It is satisfying to note the increasing number and high quality of the contributions to the surgery of the cranial contents.

The section upon suture of heart wounds contains a summary of the reported cases to date. The literature quoted upon infectious diseases shows that most of the articles during the year were

confined to clinical studies and case reports. The reports of the typhoid and pneumonia commissions are abstracted, and under scarlet fever attention is called to the opinion of several workers that the protozoan bodies described by Mallory in 1904 cannot be considered as the cause of this disease.

In the section on Diseases of Children infant foods and feeding occupy the usual prominent place, and the interesting researches by Clark, Taylor, and Prout upon "Brachial Birth Palsy," published in this JOURNAL, October, 1905, is abstracted.

Laryngology, Rhinology, and Otology contain a number of interesting abstracts. The value of such a volume as this is considerable, because though the abstracted papers are necessarily presented briefly, the reader is enabled to ascertain what various research and clinical workers are doing along the lines of progressive medicine.

OLIVER WENDELL HOLMES AND THE CONTAGIOUSNESS OF PUERPERAL FEVER. By CHARLES J. CULLINGWORTH, M.D., F.R.C.P. London: Henry J. Glaisher, 1906.

WE are sincerely glad that Dr. Cullingworth has seen fit to republish in such an attractive form this interesting address. It must be a subject of congratulation to the American medical profession to find so eminent an Englishman attributing its proper weight to the labors of his American brother. The essay is accompanied by a very short and interesting bibliography of the subject, and by an interesting portrait of Dr. Holmes, taken from a daguerreotype made shortly after the first publication of his work on the subject of "Puerperal Fever." F. R. P.

THE WORLD'S ANATOMISTS. By G. W. H. KEMPER, M.D. Philadelphia: P. Blakiston's Son & Co.

THIS little paper-bound volume is a cleverly compiled series of very condensed biographies of the most prominent anatomists who have flourished in all ages of the world's history. It includes the living as well as the dead, and it contains many portraits and some reprints of old anatomical illustrations. In such a work there are of course some omissions, and there are also some names included which might hardly seem necessary. Taken as a whole, however, the author deserves to be commended with the way in which he has performed his labor. F. R. P.

METHODS OF ORGANIC ANALYSIS. By HENRY C. SHERMAN, PH.D., Adjunct Professor of Analytical Chemistry in Columbia University. New York: The MacMillan Co., 1905.

THE book is designed to give a connected introductory training in organic analysis, and as it is largely devoted to quantitative methods for analysis of food materials and related substances, it should be found of use to those working in the sciences allied to medicine. A knowledge of inorganic quantitative analysis, elementary organic chemistry, and general analysis is presupposed. The analysis of carbohydrates, acids, oils, fats, butter, milk, proteids, and cereals are among the substances discussed. As a rule, a number of methods are given for the analysis of each substance, and the directions are thorough and clear. The book is well arranged, and the literature is extensively referred to by foot-notes and brief bibliographies at the end of chapters. G. C. R.

AERZTLICHE TAKTIK. By DR. FRITZ SCHLESINGER. Berlin: S. Karger, 1906

A COLLECTION of short essays on the practical side of professional life in the form of letters to a young physician, who, it appears, has complained to the author of the unfair concentration of practice in the hands of a few specialists and the spread of quackery. "Medical tactics" is defined as the art of winning and keeping the confidence of one's patients, which is to be attained by steadfastly bearing in mind the only legitimate object of all medical effort —the patient's welfare. The author displays a lofty sense of the duties and responsibilities of the physician and insists that sound medical knowledge, and skill born of thorough training, are indispensable to success, and that their deficiency cannot be supplied by mere superficial cleverness and "manner." Every general practitioner should make himself proficient in at least one specialty, although he need not proclaim the fact to the world. A sense of mastery in a particular field will add to the enjoyment of his work and save him from the humiliating role of a mere advisor to his patients in their selection of a specialist. As the essays deal with questions that confront practitioners of medicine the world over, their enjoyment requires no mental readjustment to foreign conditions of life, and the easy conversational style should recommend them as a pleasant relief from the heavier scientific reading to those who wish to keep up their German. R. M. G.

THE ANATOMY AND LIFE HISTORY OF ANKYLOSTOMA DUODENALE. A Monograph by A. Looss, PH.D. Translated from the original German manuscript by MATILDA BERNARD. Records of the Egyptian Government School of Medicine, No. III. Edited by the Director. Cairo: National Printing Department, 1905.

THE monograph embodies the first part of a series of studies upon ankylostoma, and deals exclusively with the anatomy of the adult parasite. After some discussion as to the history of the nomenclature, Looss determines upon the generic name Ankylostoma as the correct one, though he thinks it "abominable." The work is most exhaustive. To a description of the anatomy of the worm 143 folio pages are devoted, and eleven exquisite lithographic plates depict the structure of the parasite. There remains nothing to be said upon the subject, and as nearly as possible the author has made his work a finished study. An interesting observation is that the worm feeds solely upon the mucous membrane and submucosa of the intestinal tract, and not upon the blood of the host. If small vessels and capillaries are opened it is by accident. The monograph is a completed study. W. T. L.

TRAITMENT DE LA LEPRE PAR LE PALETUVIER, OU MANGLIER ROUGE. Par le Docteur MATIAS DUQUE, Directeur et Médecine de l'Hôpital de Syphilis et Maladies Vénériennes, San Antonio. Pp. 146. Paris: Edmond Dubois et Cie, 1905.

THIS book presents the results of the author's experience in the use of extracts prepared from the bark of the mangrove tree, which he believes to be specific in the early stages of leprosy. All patients are cured in from ten to twelve months. In the second stage, when the viscera are not yet invaded, 60 per cent. are cured within three to five years; the remainder present a more or less appreciable relief. In the third stage, when the entire organism is invaded and the viscera and nervous system are seriously affected, there is only a more or less appreciable amelioration. The neurites and neurotrophic disorders are not affected, but the diarrhœas and fevers are lessened, the appetite reappears, and the body weight increases. The evident accuracy of the detailed histories and the sincerity of purpose of the author should be rewarded by a trial of this remedy by those whose opportunities bring them in contact with patients suffering from this ill-omened disease. R. W. W.

PROGRESS

OF

MEDICAL SCIENCE.

MEDICINE.

UNDER THE CHARGE OF

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Human and Animal Trypanosomiasis.—In December, 1904, Robert Koch was sent by the German government to East Africa to study the coast fever of cattle. His opportunities led him to make observations in other diseases as well and his work is condensed in a preliminary report appearing in the *Deutsch. med. Woch.*, 1905, xxxi., 1865.

The relapsing fever of East Africa differs very little from the relapsing fever of Europe, the most striking difference being the shortness of the individual attacks and the small number of spirochætæ in the blood. The African spirochætæ, too, seem to be longer than the European form. Chromatin bodies were never seen and there was no evidence of a ciliary layer or of longitudinal splitting. There were frequently noticed, however, spaces or interruptions which gave the impression that the organisms were multiplying by transverse division. By injecting the blood from patients apes could be infected and in them the disease was very severe and often fatal. Cattle, dogs, and other animals were resistant to infection. The disease is carried by the bite of the tick Ornithodorus moubata, Murray, which lives in the floors of huts, comes out at night to prey, and hides again in the ground during the day. They are regularly found in the shelters used by caravans, but only in the portion of the ground protected from the rain. Their distribution, however, is a very wide one and they are found in parts far distant from caravan travel. After the tick has drawn blood from the infected person the spirochætæ disappear in a few days from the stomach, but careful examination shows in a large number of cases that they have become attached to the ovaries, and their number and arrangement indicate

clearly that they have undergone marked increase. After the eggs are laid many of them contain spirochætæ which show evidence of having further increased in number and the ticks developing from these are able to infect monkeys. The ticks examined for spirochætæ showed, as a rule, from 5 to 15 per cent. infected, in some instances the number running to 50 per cent. Of the three Europeans in Koch's caravan, none was taken with relapsing fever because none of them slept in the native huts or shelters. Of five native servants who did sleep in the shelters four were infected. Of the sixty-six carriers, none were infected, although they slept in the huts and shelters, evidently because they had acquired an immunity from previous attacks. Koch thinks there is evidence to show that the disease has always been endemic in East Africa and that the natives, as a rule, acquire complete or partial immunity by an infection in youth. Europeans can guard against the disease by avoiding the native huts or shelters and places where tents have been previously pitched.

Koch makes some interesting observations, suggesting the occurrence of copulation in Pyroplasma bigeminum taken from the stomach of ticks. The paragraph is well illustrated.

The parasites of coast fever differ from the well-known pyroplasma of cattle, dogs, and horses in so many respects as to suggest that they are not related to these. They do not show the division in two so characteristic of the pyroplasma, but are regularly divided into four parts, arranged in the form of a cross. Another peculiarity is that the spleen and lymph glands of cattle with coast fever contain a large number of spheroidal bodies (the nature of these bodies is not determined), consisting of bluish protoplasm in which are found many chromatin particles, and these are so constantly present before the organisms appear in the blood as to be of great importance in diagnosis. In their development, however, as seen in the tick's stomach, they resemble so closely the development of Pyroplasma bigeminum as to prove their close genetic relationship. It is noteworthy that the development of these parasites has been observed only in the tick Rhipicephalus australis, and only in full-grown, fully developed specimens. This would indicate that in coast fever infection is only carried by the young ticks.

Six of the eight varieties of the fly Glossina have been found in the German Protectorate. It has been assumed that Glossina morsitans is the carrier of tsetse disease, but Koch has shown that it may also be carried by Glossina pallidipes and indeed that Glossina fusca is principally concerned in its spread. The infectivity of these flies was shown by discovering trypanosomes in great number in the drop of clear fluid which can be expressed from the proboscis by pressure upon the bulb. Infection is not carried by the flies mechanically from one animal to another, but the trypanosomes undergo a development similar to that of the malarial parasite in the mosquito. The train of events Koch describes as follows:

The ingested trypanosomes increase in number in the stomach by longitudinal splitting and also grow in size. After a short time a marked difference is noticeable in these large trypanosomes, some developing a thick plump form, rich in blue-staining plasma and with a large round chromatin body of loose texture; others becoming very thin, with no blue-staining plasma and a long thin compact chromatin body. These forms, Koch thinks, mark sexual differentiation, the large organisms being the females, the slim organisms the males. He is not

prepared to state that copulation occurs or that, as in malaria, microgametes are formed, but there is evidence to indicate that the latter process does occur, as a rule. Further, in the wall of the stomach are found very large trypanosomes with many nuclei, probably representing further development of the impregnated female. It has not been observed, but it is probable that these organisms upon rupture furnish the youngest form of the trypanosome which has been frequently observed in infected flies. These are small spheroidal cells with a single nucleus which show all transition stages to those with nucleus and blepharoplast to which a flagellum is then added. In these young forms the blepharoplast is situated at the head end and only as the organisms advance in age does the blepharoplast pass the nucleus and lie back of it.

In the fluid expressed from the proboscis there are found regularly, besides these young and transition forms, trypanosomes which in size and appearance are identical with those in the blood of animals. It is very probable that infection results from these adult forms. Attempts to inoculate rats with trypanosomes taken from the stomach of a fly were unsuccessful.

Until Koch's work it had not been possible to infect flies by feeding them on animals with trypanosomes in the blood. If they are fed on freshly infected animals with numerous trypanosomes in the blood the organisms entirely disappear from the stomach of the fly as the blood is digested. In a few instances, however, by feeding the flies upon animals that had been infected a long time before and in which trypanosomes appear in the blood only occasionally and in small number, the experiment was successful. This indicates that not all trypanosomes can infect Glossina, but only those in some special condition of which we know nothing. This condition seems to be best realized in animals little susceptible to the disease, as buffaloes and antelopes. Both males and females of Glossina prey upon animals and can infect by biting others. The females do not lay eggs as other diptera do, but only a single white larva which becomes a pupa in a few days. From ten to twelve days elapse between the laying of larvæ, so that reproduction is very slow. This, Koch thinks, is the weakest point in the chain of trypanosome infections and the point where the attack may yield the best results.

The Experimental Production of Aneurysms.—BERNARD FISCHER (*Deutsch. med. Woch.*, 1905, xxxi., 1713). Since Koester's contention that aneurysms are always due to a circumscribed lesion of the media most of the work upon aneurysms has confirmed his view. A primary tearing of the elastic fibres by high blood pressure has not been satisfactorily established. Experimentally traumatism is never followed by aneurysm formation. Any wound or injury to the arterial wall heals completely and there is not even a local dilatation left to mark its position. Fabris, however, by the use of corrosive substances, has succeeded in producing local necrosis of the vessel wall followed by the formation of true aneurysm, and Josué has produced arteriosclerosis and atheroma without any local insult by repeated intravenous injections of adrenalin. The process in these adrenalin cases, however, is quite different from that in human arteriosclerosis, being due to a primary necrosis of the musculature and elastic lamellæ in the media. Fischer has shown that many poisons are capable of producing this arterio-

necrosis and that it may even arise spontaneously in cachectic rabbits. But the condition is never as general or as well-marked as in animals treated with adrenalin products. These facts demonstrate that a toxic influence upon the musculature plays an important part in the production of arterionecrosis, but that the enormous functional overtaxation upon the arterial system by the high pressure from adrenalin is also of great importance. Of these various toxins, adrenalin was, until recently, the only one which would carry the process far enough to give rise to the formation of genuine aneurysm of the arch. Recently, Fischer has had success using digalen.

The character of the lesion in aneurysm is merely that of further development of the arterionecrosis. The beads which are seen projecting into the lumen of the vessel represent areas of calcified necrosis. These areas are situated chiefly in the centre of the media, seldom reaching quite to the intima, practically never to the adventitia. The middle and inner half of the media are the positions of selection. While the pressure is maintained in the vessel these beads are represented by local dilatations; when the pressure is removed, it depends merely upon the extent of the lesion whether there will be a protrusion or a small aneurysm. If the outer portion of the media is intact the contraction of the muscle fibres and the outer elastic lamellæ cause the protrusion of the calcified media. If the lesion is more extensive and the elastic fibres have undergone degeneration the depression remains even after the pressure is removed. The calcification, Fischer thinks, is a protective feature, believing that the aneurysm would follow more quickly if it were not deposited.

These results which he has obtained upon rabbits cannot be directly referred to man. Similar experiments in dogs gave only negative results. Fischer thinks, however, that they testify to the unequivocal importance of disease of the media in the formation of aneurysms and emphasize, too, the importance of high blood pressure.

While the process in these cases is different from that in genuine arteriosclerosis, Fischer thinks they are opposed in some points to Thoma's views on the formation of arteriosclerosis. As is well known, Thoma insists upon a histomechanical basis, namely, that when the blood flow is slowed there is a connective-tissue overgrowth in the intima. In various grades of dilatation which must have occasioned a masked retardation of the blood flow, Fischer was never able to find evidence of thickening of the intima, even after long standing. Such a thickening he finds only in the presence of inflammatory reaction about the necrosis. He also draws attention to the curious location of the poisonous effects. Only the smooth muscle of the media is attacked, and not even this diffusely, but only in well-circumscribed areas.

The Occurrence of Sudden Death in Families Due to Status Lymphaticus.—Ernst Hedinger (*Deutsch. Arch. f. klin. Med.*, 1905, lxxxvi., 248) reports the interesting occurrence of sudden death in a child five years old who at the autopsy showed well-marked lesions of status lymphaticus. The patient was the fifth child in a family of nine to die suddenly and under similar conditions. This tendency of the children of certain families to sudden death is referred to as early as 1614 by Felix Plates, who cites the instance of a five months' child dying suddenly in an attack of dyspnœa, two children of the same family having previously succumbed with the same abrupt and unexpected symptoms. Weber

refers to a family in which two nurslings had died suddenly with symptoms of suffocation, and the third child, five months old, dying under the same condition, showed at autopsy marked hypertrophy of the thymus. Barrock records in one of his cases that two children in the same family had been found dead in bed without having shown any previous symptoms of illness.

Friedjung refers to a six months' old child dying from hyperpyrexia during an otherwise inconsiderable febrile disturbance and showing at autopsy marked status lymphaticus. A brother of these children, had died suddenly when a few months old, during convalescence from a slight intestinal catarrh.

Avellis reports two cases of inspiratory stridor in the same family, and Schmidt a family in which four children suffered from the chronic stridor of infancy and three died of it. There were, however, no autopsies to substantiate the view that the attacks were due to an enlarged thymus. Perrin reports a family in which nine out of eleven children died suddenly.

Hedinger's patient was a girl, born December 27, 1893, who developed normally and grew up in apparently perfect health. In March, 1899, the child, while at play, suddenly fell unconscious and became extremely cyanotic. During the attack, which lasted two to three hours, curious high-pitched notes were ejected. After a few days the child had recovered completely. On September 21, 1899, while in the fields harvesting potatoes, she again suddenly fell unconscious and died after a few gasps. At autopsy marked enlargement of the thymus and of all the lymph glands of the body was found, and striking hyperplasia of Peyer's patches and the solitary follicles of the digestive apparatus, marked swelling of the tonsils, enlargement of the spleen, and considerable eccentric hypertrophy of the left ventricle. There was marked hyperæmia of most of the organs, particularly of the abdominal organs. Microscopically, the follicles of the lymph glands and spleen showed a marked enlargement of the germinal centres and in the spleen the veins were crowded with lymphocytes. The medullary portion of the thymus was particularly enlarged and many of the vessels richly filled with lymphocytes. Hedinger believes he has observed in these and other cases of status lymphaticus numerous changes which point to a transition between status lymphaticus, pseudoleukæmia, and leukæmia.

The particularly interesting thing in Hedinger's case is the family history. As has been stated, four children had previously died in the same family with identical symptoms. The first, a boy of five years and three months, always healthy, died in the first attack. The second, a girl in her sixth year, who had always been well except for repeated attacks of tonsillitis, died suddenly while at play. The third, a girl of three years and sixteen days, died similarly. She had previously suffered from frequent but not severe attacks of diarrhœa. The fourth, a boy of five years and four months, died in the fields in his third attack. Four children are alive and well; three were always healthy: eight, nine, and eleven years old respectively. The fourth, a three-year-old child, had at the age of two years a mild attack of cyanosis, from which she recovered and has remained quite well since. The parents were perfectly healthy. They were nearly related, their fathers being brothers. The father of the children was a heavy drinker. No attempt is made to explain this tendency in certain families toward hyperplasia of the lymphatic system.

SURGERY.

UNDER THE CHARGE OF

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Transdiaphragmatic Massage of the Heart in a Case of Apparent Death in the Newborn.—VANVERTS (*Annales de la Société Belge de Chirurgie et Journal de Chirurgie*, October, 1905) was called in consultation in a case of difficult labor. The fœtal heart sounds were rapid but strong. Version was performed. During the disengagement of the arm the child made an inspiration in utero. When born it was apparently dead. The heart-beat could not be detected, but in the epigastric region there was a continual trembling movement. Artificial respiration, "mouth to mouth," for twenty-five minutes and hot baths were without result. The epigastric tremors continued.

Through an incision along the left costal border two fingers were introduced into the abdominal cavity. When they touched the diaphragm an inspiration occurred. Rhythmical massage of the heart was then carried out by compressing it between the fingers inside and the other hand on the chest outside. No cardiac contraction was felt at any time. From time to time for five minutes an inspiration took place, the interval while not accurately observed being from a half-minute to a minute. At the end of five minutes they disappeared entirely, the epigastric tremors ceasing also.

The writer emphasizes two points in this case: (1) The cardiac massage did not produce a cardiac contraction: the only result was faulty respiration for a short time. (2) The first inspiration, excluding that which occurred in utero, was produced when the fingers touched the diaphragm and before the heart was compressed. The writer thinks that in these conditions, although a cardiac contraction may occur later, it is the touching of the diaphragm and not the cardiac massage which originates the reflex causing the first inspiration. If this is so, then this paper should have been entitled "The Production of Inspiratory Movements by Excitation of the Diaphragm."

The Ventral Decubitus in Surgery.—LAMBOTTE (*Annales de la Société Belge de Chirurgie et Journal de Chirurgie*, October, 1905) believes that the introduction of the ventral decubitus marks an important advance in surgery, and that the operative technique and the indications for many operations will be modified by it. It is applicable to all operations on the posterior surface of the body; as trephining in the occipital region, operations on the back of the neck, shoulders, vertebral column, lungs, posterior surface of the liver, sacrum, pelvic organs, and the posterior surface of the extremities.

The patient is first anæsthetized in the dorsal position and then turned absolutely on his face. The arms are permitted to hang from the sides of the table and the extremities to remain in the extended position or to hang from the table according to the necessities of the case. Pads or cushions may be used to elevate this or that part of the body, when desired. Anæsthesia is remarkably easy in this position as compared to the lateral, which Lambotte finds to be a striking advantage in empyema operations. Some cancers of the rectum operated on successfully in this position had been considered inoperable by the old methods. The sacral route offers great advantages for the removal of cancer of the uterus. Two operations were performed for double kidney involvement. One was a double decortication, and the other a double decortication and nephropexy. No change in position is necessary during the whole operation. He reports twenty operations of various kinds done by this method.

Observations on the Removal of the Vermiform Appendix.—KOLLIKER (*Zentralblatt f. Chirurgie*, October 14, 1905) says that he has made use of an incision, during the past year, which produces a slight wound, and guards against ventral hernia later, as effectually as does the suture of the wound in layers. It is a slightly oblique incision, beginning at McBurney's point and running in the direction of the symphysis pubis for about 8 cm. After the division of the skin and subcutaneous tissues the aponeurosis of the external oblique muscle and the anterior layer of the sheath of the rectus for its outer third or half are divided. The border of the rectus muscle is then separated from its sheath and held aside by a retractor. The tendinous fibres of the internal oblique and transversalis fascia as well as the transversalis are then separated. The incision in the peritoneum is made small, 3 to 4 cm. This incision has the advantage that the peritoneal portion of it lies chiefly under the rectus muscle, and that no muscle has been divided except a few tendinous fibres of the internal oblique and transversalis. In the closing of the wound the peritoneum is sutured separately and the rectus muscle overlies the suture. A second suture seizes all the other layers together.

If after opening the abdomen the visceral relations are distorted and the search for and separation of the appendix gives trouble, the incision can be lengthened at both ends in order to give a better view of the relations. For these cases Kölliker calls attention to two points. The position of the appendix can easily be found if the cæcum is freely exposed and the anterior longitudinal band of the cæcum is followed carefully. The twisted appendix draws the longitudinal band in its direction. If the internal band is convex it speaks for a retrocæcal position of the appendix. If the external longitudinal band is convex then the appendix is situated on the inner side of the cæcum or in the pelvis. Zuckerkandl considers that these varieties are physiological; Kölliker believes that they are due to inflammatory changes.

The Etiology and Treatment of Hernia in Adults.—RUSSELL (*Intercolonial Medical Journal of Australia*, September 20, 1905) says that acquired hernia does not exist in children; that it is invariably dependent upon the presence of a congenital sac, which in the great majority of cases is provided by some portion of the process vaginalis. Only by the complete removal of the sac from the inguinal canal can the

hernia be cured, the so-called curing of the hernia by the use of a truss being a deceptive misnomer.

The writer believes that the direct inguinal, femoral, obturator, and all varieties of hernia other than traumatic are due to the presence of a congenital peritoneal pouch. The best test of this is the fact that the simple removal of the sac cures the hernia in children. The writer has applied the same test in eighty-nine adult herniæ. The canal was not closed by sutures, except in one or two of the earliest cases. The list includes subjects of all ages and herniæ of various duration. Of the eighty-nine cases, twenty-six could not be traced. Of the sixty-three remaining, recurrence took place in three, taking one year's immunity as the standard of success. Russell agrees with Deanesley that recurrence, if it occurs at all, does so in the vast majority of cases within the first six or eight months from the time of operation. In adults, unlike children, because of the length and obliquity of the canal, it is not possible to get at the peritoneum, at or above the internal ring, without slitting up the external oblique. In adults from prolonged stretching and dilatation the canal becomes converted into a large hole in the abdominal wall. Any portion of the peritoneum exposed below the muscular border of the internal oblique and transversalis must be considered a part of the sac and removed. The transversalis fascia should be included in the ligature closing the sac, the inner part of which, especially, is to be drawn up by the ligature. Sutures of the muscles are not necessary, the essential for success being the removal of the sac.

Simplified Operation for Hernia in Children.—HERRING (*Intercolonial Medical Journal of Australia*, September 20, 1905) has devised and practised as a corollary to Mr. Russell's theory (see above) a method of shortening the radical operation for hernia in children. The sac is exposed and opened in the usual way, the contents are reduced into the abdominal cavity, and the incision having been extended to the neck, the sac is turned inside out, exposing the peritoneal surface. The neck of the sac is then divided transversely and the upper cut end closed. The wound is then closed by a subcuticular suture. The sac, having been turned inside out, is left to shrivel up quietly, and an operation ordinarily requiring three-quarters of an hour is reduced to one taking a few minutes.

The Treatment of Racemose Arterial Angioma of the Scalp.—KROGIUS (*Zentralblatt f. Chirurgie*, September 30, 1905) has employed the following treatment, with success, for cirsoid aneurysm of the scalp. He used two needles, each furnished with a handle, one handle having a slightly curved needle, the other a more marked curve. Both were capable of bending considerably. The needle with the greater curve was passed through the skin to the skull, then along this for a short distance and out through the skin. After being threaded with a strong catgut ligature it is withdrawn, leaving the ligature in position. Through the same point of entrance the second needle is passed and its point made to emerge at the second opening, the track of the needle being just under the skin. The end of the ligature at the second opening is now threaded into the needle and withdrawn through the first. The ligature, which includes in its loop the thickness of the scalp, excluding

the skin, is now tied at the first opening and the ends removed. Other such ligatures are placed, one close to the other, so as to form a chain-like series around the whole tumor, thus shutting off the greater part of its blood supply and causing a shrinkage of it. If the first operation is not a complete success, and more or less of the angioma is left, a second smaller ring of ligatures may be applied around the remaining part of the tumor. The operation may be repeated until the angioma has entirely disappeared.

Four Unusual Cases of Aneurysm.—LOCKE (*Boston Medical and Surgical Journal*, December 14, 1905) says that the first patient was a man, aged thirty-six years, who had syphilis in youth; tuberculosis of both hips for twenty-five years; double inguinal hernia; marked arteriosclerosis; relative mitral insufficiency; tabes dorsalis; chronic interstitial nephritis; deformity of the spine; and aneurysm of the left axillary artery, possibly following trauma, which reached an enormous size and finally ulcerated externally, with death after five days.

The second patient, a colored woman, aged sixty-six years, had arteriosclerosis; aneurysm of the transverse aorta, the first sign of which was hæmatemesis. Nine days later she had a second attack, with death after ten hours, from ulceration and hemorrhage into the œsophagus at the level of the bifurcation of the trachea.

The third patient, a man, aged thirty-six years, had syphilis twelve years ago, and later developed a sacculated aneurysm of the abdominal aorta, with rupture into the retroperitoneal tissue and subsequent erosion of the vertebræ, hydrothorax, atrophy of the left kidney, and arteriosclerosis. An exploratory laparotomy showed a large pulsating tumor occupying the entire upper left quadrant of the abdomen. He was doing well five days later, when he suddenly collapsed with signs of hemorrhage, four months after the onset of the symptoms.

The fourth patient, a male, aged eighty-one years, showed general arteriosclerosis, multiple aneurysm of the abdominal aorta with ulceration into the third portion of the duodenum, and hemorrhage into the stomach and intestines. The symptoms extended over a period of four months. Death occurred four days after rupture.

Contribution to the Surgery of the Prostate Gland.—BARKER (*New York and Philadelphia Medical Journal*, December 16, 1905) thinks that the time when prostatectomy should be done should be settled as definitely as it has been settled for appendicitis. The use of the catheter by the patient should be condemned, because infection invariably follows, and because it encourages the patient to put off the operation until what should be a benign operation becomes a dangerous one. By early operation years of invalidism are avoided. Three essential points in the operation should be aimed at: minimizing the loss of blood, a short operation, and the least possible traumatism. Barker prefers the perineal operation by an inverted U-shaped incision, beginning two-thirds of the distance between the anus and the tuberosity of the ischium, carrying it over the bulb of the urethra and back to a corresponding point on the opposite side of the anus. It affords the maximum of room, enables the operator to see every step of the operation, and avoids the angular flap of the inverted Λ incision. The various steps of the operation are then described. The sphincter

is divided early in the operation, and later sutured in position again. The membranous urethra is divided on the grooved staff, a special prostatic tractor is introduced into the bladder and its blades opened. By elevating the handle as a lever and using the pubes as a fulcrum the prostate is brought into the operative field and enucleated. To break up the tough bands firmly uniting the gland to the capsule a forceps, with teeth, is used as a tissue crusher. A good-sized drainage tube wrapped with gauze is introduced into each lateral cavity and brought out of each of the two lower corners of the wound. As large a catheter as possible is introduced through the penis into the bladder and retained, for the escape of urine into a urinal and for washing the bladder. The drainage tubes are removed in forty-eight hours. The writer has treated thirty cases in this way, losing one patient who died of senile pneumonia. As for the retention of virility after the operation, so far as he knows, no one has reproduced after this operation.

A Note on Prostatectomy for Hypertrophied Prostate.—LOUMEAU (*Annales des Maladies des Organes Genito-Urinaires*, December 15, 1905) believes that the total transvesical prostatectomy of Freyer offers little opportunity for improvement, judging from his own short experience and the brilliant and abundant results of the promoter of the operation. In four cases, however, in which he diagnosed hypertrophy of the lateral lobes, he failed to enucleate these lobes by the method of Freyer. By cutting through the inferior bladder wall at the summit of each prostatic lobe, with the right index finger through this incision he was able to isolate and extract the lobes. He considers that the transvesical enucleation of a sound and normal prostate is wellnigh impossible. On the contrary, an adenomatous gland, even if very small, can be perfectly enucleated, although this will be much more difficult than in the case of an hypertrophy of large dimensions.

On Some Recent Advances in Urology.—HEITZMANN (*Boston Medical and Surgical Journal*, December 21, 1905) says that the most frequently employed new method of recent years is cryoscopy. This is the determination of the freezing point of blood and urine, which varies according to the number of molecules a solution contains. It is not entirely trustworthy. The methylene blue, phloridzin, electric conductivity, and toxicity tests are not at all reliable. No surgeon should determine upon the removal of one kidney before he has satisfied himself of the functional activity of the other, but no unanimity as to the method to be employed has yet been attained. When the examinations are carefully conducted the microscope is undoubtedly of extreme aid in the diagnosis of many lesions of the genitourinary tract, as the majority, though not all, epithelial cells in the urine are characteristic enough to admit of their location. Not only can nephritis be diagnosed when true tube casts are not present, but also pyelitis, ureteritis, cystitis, prostatitis, and other inflammations, as well as suppurations, ulcerations, and many other conditions. One may judge the constitution of the individual by the character of the pus corpuscle. Microscopic urinalysis of catheterized urines of separate kidneys is much more trustworthy than other methods of determining the functional condition of the kidneys.

A Case of Acute Hemorrhagic Pancreatitis; Operation; Recovery.—JONES (*Liverpool Medico-Chirurgical Journal*, January, 1906) made a diagnosis of some gastric lesion, possibly a perforated gastric ulcer. On opening the abdomen about three pints of free fluid, bright blood mixed with serum, issued from the cavity. The presence of fat necrosis at the entrance of the lesser peritoneal cavity led to an opening through the gastrocolic omentum, which disclosed a discolored œdematous and in places hemorrhagic pancreas. After cleaning out the blood and packing around the pancreas with gauze a longitudinal incision was made in the pancreas. No stone, abscess, or other cause was found. The cavity in the pancreas was packed with gauze, which was brought out of the wound. This was carefully removed in thirty-six hours, being followed by a discharge of clear pancreatic fluid which gave trouble at the upper part of the abdominal wound. Healing was complete, and the patient discharged cured in about ten weeks after the operation.

Cholerrhagia in Hydatid Cysts of the Liver.—TERRIER and DUJARRIER (*Revue de Chirurgie*, January 10, 1906) says that cholerrhagia after the marsupialization of hyatid cysts of the liver is a frequent complication. Two forms should be distinguished: (1) Partial cholerrhagia, much the more frequent, which ceases spontaneously in a variable time, without notable disturbance of the process of healing. (2) Total cholerrhagia, much less frequent without being very rare. It is sometimes accompanied by very grave symptoms and may be fatal. As a rule, it undergoes spontaneous cure, but in some cases it may demand a serious operation to save the patient's life. The writers report three cases of this kind from the literature, which were all that they could find.

That this condition exists before operation is shown by the fact that on opening it the cyst is found to contain bile. It was formerly claimed that bile in a cyst would cure it, and that the bile would kill the parasites. Dévé cites a case in which a cyst ruptured into the biliary passages, and the daughter cysts were engrafted on and continued to live in the biliary ducts. In some cases the cholerrhagia occurs at the time of operation. It occurs much more frequently in the first twenty-four hours, its presence being detected at the first dressing. It is also frequently seen some days or weeks after the operation. In other cases it occurs late when there remains only a fistula, or even after complete cicatrization of the wound. In a case of Kehr's the common bile duct became blocked and the increased pressure in the biliary paths caused the scar to yield with an escape of bile (secondary or consecutive cholerrhagia).

Between the partial and total varieties all grades occur. When total the absence of bile in the feces shows that none is passing into the intestines. In such cases the dressings may be saturated several times a day. The disappearance of the cholerrhagia depends on one of two facts: the closing of the wound in a biliary duct, or the elimination of a biliary obstruction. Suppuration does not appear to play an important part in its causation. When the condition lasts a long time the patient succumbs either to a progressive cachexia or to an intercurrent complication which he cannot withstand. When due to trauma the cause is easily explained, the biliary passages being opened at the time of the

operation, or during the dressing by a forceps, a drain, or a trocar. In the greater number of tardy cholerrhagias, appearing months after operation, at times after the cicatrization of the wound, the cause will be some obstacle in the biliary passages. This may be an obstruction by daughter cysts, a tumor, or inflammation of the common bile duct or ampulla of Vater.

The treatment should be prophylactic and curative. The prophylactic consists in avoiding as far as possible injury to the often denuded, dilated, and friable biliary canals, especially in the removal of the parent membrane of the cyst, and in avoiding unnecessary interference afterward. In the suppurating cysts the membrane is more adherent and requires more care in its removal.

Abscess of the Liver and Precocious Cholerrhagia.—VALENCE (*Revue de Chirurgie*, January 10, 1906) says that precocious cholerrhagia is the escape of bile, pure or mixed with pus, during the twenty-four hours following the incision into an abscess of the liver. It is distinct from primitive and secondary cholerrhagia. The secondary variety occurs when the biliary canals have opened into the pus cavity by the separation of the sloughs, that is, some days after the operation. It ceases when the process of repair is sufficiently advanced. Thrombi of the biliary vessels may also be dislodged by the pressure of the biliary current. Valence believes that with care the drains ought not to produce cholerrhagia, from the hypersecretion of irritation, nor by ulceration into the biliary vessels. Irrigation of the abscess cavity is not responsible for precocious cholerrhagia, since this occurs before the first change in the dressings is made. Of four cases of the precocious variety, collected from the literature, in only one case was curettage done, so that this is not the essential cause.

Bertrand considers that a cholerrhagia is a serious symptom, and is to the biliary vessels what hemorrhage is to the bloodvessels. When excessive it tends to ruin the nutrition. The writer attributes a costal caries in this patient to the dissolving action of the bile which came in contact with it. Catgut sutures will yield to its influence. Fontain advises that the abscess should be opened widely, to permit rapid and complete evacuation, to avoid infection, and to favor prompt cicatrization. This would be the best means of abridging the duration of the biliary flow, and of attenuating its effects. The treatment for hemorrhage under the same circumstances should be carried out (thermocautery, tampon of iodoform gauze, and a gelatin solution of 1 to 10 per cent.). The writer believes that eversion of the edges of the abscess by suturing them to the skin, although adding to the time of the operation, is a good precaution against necrosis from the action of the bile. The skin should be protected from the bile by a smearing of vaselin. Internal treatment must be directed against the failure in nutrition and emaciation.

Two Cases Illustrating Sciatica of Abdominal Origin.—Ross (*Lancet*, January 13, 1906) reports that in one case the removal of a small, exceedingly tense, central cystic tumor of the left ovary, about the size of a small orange, was followed by a complete disappearance of the symptoms of sciatica. The operation on the second patient resulted in death, but it was evident that a large tumor of the uterine cervix acted mechanically in producing the sciatica.

Some of the Advantages and Fallacies of Urinary Examinations.—SAVIDGE (*Boston Medical and Surgical Journal*, December 21, 1905) says that in almost all patients over forty who put the tension of concentration on their vasomotor system, faint traces of albumin can be found if the urine is examined often enough. This is especially noticeable with those who have overdeveloped venous calibres, whereby the extra capacity of the veins keeps an undue share of the whole volume of the blood in the veins as sewerage blood.

Certain forms of therapeutics can vary the specific gravity of blood; the output of urea can compass the solution of crystals which, like pepper in the eye, must irritate the delicate kidney substance and point to sure future trouble; and in these relaxed venous cases can even remove albumin by enhancing the tonicity of the veins.

Having thus seen the relation between arterial tension by repeated laboratory use; between venous tonicity and albumin; between specific gravity and the appearance and disappearance of hæmoglobin; the following conviction has grown: varying these conditions will vary the laboratory findings; and the conditions may exist and be perfectly observable some time before the laboratory will give any finding.

THERAPEUTICS.

UNDER THE CHARGE OF

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Serum Therapy in Scarlet Fever.—W. K. METCHNIKOFF reports upon thirty patients treated by means of serum. In ten Moser's serum was employed and in twenty a serum was used that had been prepared by Professor Sawtscheuko, in the laboratory of the University in Kasan, at the children's clinic of which the treatment was carried out. All types of the disease were in the series and there was but one death, recovery without permanent complications occurring in the other instances. In the severe forms injections of six ounces or slightly more were given and were well borne, the pain at the site of injection seldom lasting longer than twenty-four hours. The influence of the treatment upon the course of the disease was most favorable, the temperature became lower, the pulse stronger, and the respiration slower; after from twelve to twenty-four hours the nervous symptoms would become less marked and the throat manifestations ameliorated. The serum, while it did not seem to prevent complications, rendered their course mild and favorable. Albuminuria was noted in four of the patients treated by Moser's serum,

while more of those who received the other serum exhibited nephritis. No glandular suppurations nor complicating otitis occurred. The most constant sequel of the injections was an urticarial or a morbilliform rash which lasted at most but two weeks and was sometimes accompanied by slight rise in temperature. Œdema of the face and arm was observed in two instances. Glandular enlargements were rare and evanescent and joint pains were seldom noted. As indications for the repeated use of the serum the author gives continuation of high temperature, small and rapid pulse, and poor general condition.—*Wiener klinisch-therapeutische Wochenschrift,* 1905, Nos. 49 and 50, pp. 1223 and 1253.

Treatment of Leukæmia.—O. F. F. GRUNBAUM states that during the past three years leukæmia has been treated by the *x*-rays, the light being applied to the ends of the long bones and over the spleen. The treatment seems to have been empirical, but since it has been apparently successful in a number of cases, Helber and Linser have investigated the effect of the *x*-rays upon the blood of healthy animals. They found that the leukocytes in the blood of rats were destroyed by an exposure of five to ten hours. In larger animals the effect was slower. The lymphocytes suffer most while the red cells, blood plaques, and hæmoglobin are insignificantly affected. The usual *x*-ray treatment of leukæmia consists in an exposure of ten to twenty minutes on alternate days; seldom are any unpleasant symptoms caused and the improvement, especially at the beginning, is often striking, the increase in hæmoglobin being rapid and the diminution in the leukocytes most satisfactory. The white cell count, conducted just after exposure, will, at the beginning of treatment, result in an estimate higher than the average throughout the day and in one below the average after treatment has been continued for some time. With the improvement in the blood there is often diminution in the size of the spleen, which is said to be less in chronic than in recent cases. Even those patients in whom the blood becomes practically normal are liable to relapse, and none, so far, has remained well for a sufficiently long time to be considered cured. Dock asserts that no stronger claim can be made for the *x*-rays than for arsenic. The author has observed two patients who failed to improve under the *x*-rays, and who reacted well to arsenic.—*The Practitioner,* 1905, No. 450, p. 767.

Epilepsy and Dechloridation.—CH. MIRALLIE considers that this form of treatment is a great advance in the therapeutics of epilepsy. He concludes a large number of observations with the following *resume:* The diet with diminished chlorides in depriving the nerve cells of sodium chloride renders them more susceptible to excitants and increases their susceptibility to sedatives. In the face of these facts it is necessary to guard all patients undergoing this treatment from exciting influences. This form of diet is an excellent adjuvant to the bromide treatment, since when it is instituted we can, in many cases, obtain results with small doses of bromides equivalent to those obtained with large doses in connection with ordinary diet. Frequently epileptics seem to have a particular appetite for salt; it is principally in such that this type of treatment yields best results. An absolute milk diet is the great aid in accustoming the patients to the regimen from which salt is omitted.—*Gazette médicale de Nantes,* 1905, No. 41, p. 809.

Guaiacol in Renal Tuberculosis.—M. SCHULLER reports two patients whose urine contained tubercle bacilli, and whom he has treated, with excellent results. He gives the drug internally, in doses of 12 to 20 drops, five or six times a day in one-half to one glass of boiled water, and at the same time injects a mixture of guaiacol and iodoform subcutaneously. The internal administration of the drug is continued for a considerable number of months. One of the patients reported was a man with tuberculous orchitis, and the other a child, of three and one-half years, with coxalgia and renal tuberculosis. The guaiacol-iodoform mixture was injected into the hip and at the same time guaiacol was given internally. A year after the beginning of the treatment the hip lesion had cleared up, the patient had gained twenty pounds, and was in excellent health. The urine contained no tubercle bacilli, and the patient was considered cured. After eight years of experience with this form of treatment the author has noted no resulting disturbance of the urinary apparatus.—*La Semaine médicale*, 1905, No. 41, p. 491.

The Diet Lacking in Chlorides in Infantile Nephritis.—G. ARAOZ ALFARO in a paper based upon the results obtained in a number of cases concludes that in children affected with acute nephritis or with acute exacerbations of chronic nephritis the elimination of sodium chloride by the kidneys is more or less disturbed, and if this substance is not excreted by other organs a condition of retention results. The retained salt is prone to cause an interstitial œdema and effusions into the serous cavities. The re-establishment of chloride elimination through the kidneys usually causes a rapid amelioration of the nephritis. The polychloruria indicates the phase of œdema resorption. Since œdema plays a considerable, if not an exclusive, part in the production of the so-called uræmic disturbances it is absolutely essential to withdraw as much as possible of the chlorides which are being introduced into the organism. It is the lack of these substances that explains the classic employment of the milk diet in nephritic conditions. It is, however, easy to arrange a diet which shall contain less salt than milk alone, such as one composed of meat, bread, butter, and vegetables, either associated or not with milk; this is especially indicated when milk is not well borne, and is of great aid in combating the anæmia which is so constant in nephritis. Such a mixed diet without salt, but containing a considerable amount of meat, is well tolerated and is extremely active in combating the œdema and uræmia symptoms.—*Annales de la Policlinique de Paris*, 1905, No. 10, p. 222.

Potassium Iodide in Small Doses in Vasomotor Rhinitis.—C. J. KOENIG reports a case of this affection in a young woman of twenty-one years, which had resisted all forms of treatment. The symptoms were paroxysms of profuse serous discharge, nasal obstruction, frontal headache, conjunctival congestion, etc. He prescribed a 5 per cent. solution of potassium iodide, of which a coffee-spoonful was to be taken in a little milk after the two principal meals. From the beginning of the treatment the crises ceased and cure has been permanent for six months, only occasional snuffling and slight nasal obstruction remaining. As a precaution the author suggests taking the iodide three times a year for a month at a time.—*La Semaine médicale*, 1905, No. 42, p. 500.

The Treatment of Lobar Pneumonia.—Leopold Bayer reports rather remarkable results in ten cases of lobar pneumonia from the following prescription: quinine hydrochloride 2.5 grains, sodium salicylate 5 grains, of which the dose is three or four powders daily. The treatment is harmless, and acts as well in severe cases in old persons as in milder types of the disease. The author has observed improvement in some instances after the administration of the first dose, and considers that this treatment sometimes shortens the disease.—*Therapeutische Monatshefte*, 1905, No. 11, p. 579.

The Treatment of Conjunctival Diphtheria.—G. Sourdille concludes a paper upon this subject with the following statements of M. Dugast: The antidiphtheritic serum of Roux injected beneath the conjunctiva of rabbits has no marked local reaction. It does not seem to neutralize the local condition due to the toxin of the infection if the dose is insufficient to immunize the whole body of the animal. Hypodermic injections of antidiphtheritic serum is the only effectual method of treating conjunctival diphtheria. Instillations and subconjunctival injections of antitoxin seem futile. For local treatment irritants should not be employed, either as irrigations or as applications. We should use either sterile water or mild solutions of boric acid, sodium hyposulphite, or potassium permanganate (1 to 3000). Friction, massage, etc., should not be employed to remove the false membrane. In the prevention of corneal complications early injection of antitoxin is most efficacious, and it is necessary carefully to avoid all procedures which may disturb the integrity of the epithelium either chemically or mechanically. If ulceration occurs antitoxin should be administered again and may be repeated daily if necessary. Careful irrigation with mild antiseptics and instillations of 1 to 2000 methylene blue should be given, and after the acuity of the attack collyria of atropine and of pilocarpine may be employed.—*Gazette médicale de Nantes*, 1905, No. 40, p. 781.

Xylol in Smallpox.—M. Joseph Belin has treated variola by the usual means, in addition giving 100 to 120 drops of xylol during the twenty-four hours. For children he prescribes from 15 to 40 drops per day, depending upon the age. The usual mortality of 24 per cent. was reduced by this treatment to 12.5 per cent. Complications were also reduced and the tendency to pitting, as well as the characteristic odor of the disease, were lessened. These results, according to the author, confirm the observations of others and demonstrate the superiority of this form of treatment. M. P. Teosier also testifies to the advantages of the xylol as a deodorant, and states that it tends to arrest or shorten the period of suppuration. He considers this to be the treatment of choice in variola.—*Revue française de Médecine et de Chirurgie*, 1905, No. 45, p. 1071.

The X-rays in Leprosy.—H. B. Wilson reports the results of the treatment by the *x*-rays of fourteen patients suffering from leprosy. Of these three have been considered cured, seven improved, and three not improved. The author is inclined to believe that when a local lesion of leprosy is treated with the *x*-rays the organisms there localized are killed and their bodies are absorbed by the system, producing an immunity against the living organisms. In support of this theory he

cites the following facts: (1) The treatment of one leprous spot causes improvement in other distant lesions. (2) The cure in the distant spots seems to progress with, and to be just as complete as in, the lesion actually treated. (3) The best results seem to be obtained only when the treatment is pushed to the point of destroying or beginning to kill the tissues, which would also probably be to the point of killing the organisms. (4) Subjects in whom there are massive localized deposits improve most rapidly since here we have abundant culture on which to operate and produce immunity. (5) In diffuse general involvement of slight grade or of atrophic character in which there are but a few organisms the author has had but little success. (6) In two patients with advanced leprosy, with a large amount of new leprotic tissue, the improvement was marked and rapid, but was followed by loss of general health and rapid physical decline. The treatment was carried out as follows: The part presenting the greatest amount of leprotic deposit was selected and exposed to the rays ten minutes at a distance of seven to ten inches. The time and distance were varied from time to time, the effect being made to approach as near to burning the skin as possible without actually doing so. The treatment causes a slight tickling sensation; after two or three exposures a blushing of the skin may or may not occur and a sensation of itching is noticed. Burns necessitate the temporary suspension of the treatment.—*Journal of the American Medical Association*, 1906, No. 5, p. 315.

The Roentgen Rays in Glandular Tuberculosis.—J. BERGONIE writes with some enthusiasm concerning the favorable action of the *x*-rays in glandular tuberculosis. He employs the following method: The tube is placed at a distance of 10 centimetres (about three inches) from the lesion; the exposure is for about five or six minutes, depending upon the condition of the skin; the surrounding tissues are protected by a shield of lead. Treatment is applied every five or eight days, depending upon the cutaneous reaction: properly the skin should first be rose color, then red, and then brown. The rays used are No. 5 or 6, as gauged by the radiochromometer of Benoist, and the treatment lasts from one to three months. Most favorable results have been obtained; the masses of glands diminish in size, the glands become discrete and many disappear, others remaining are of small size but difficult to find and freely movable under the finger. The author suggests the employment of the rays in tuberculous inflammations of the bronchial glands.—*Journal de Médecine de Bordeaux*, 1905, No. 47, p. 825. (Personal experience does not confirm these observations. —R. W. W.)

Lymphatic Leukæmia and Radiotherapy.—M. RENON has followed for several months a patient suffering from lymphatic leukæmia while undergoing *x*-ray treatment. He has observed that, while there was a noticeable amelioration of the general condition, a considerable diminution in the numbers of lymphocytes, a resolution of the glandular enlargements, and a decrease in the size of the spleen, two factors were present which led him to feel discouraged concerning the ultimate result. There were a diminution of the hæmoglobin and of the red cells and a progressively increasing temperature. While the white cells were diminished from 873,000 to 31,000, the red cells fell from 1,428,000 to 640,000. The temperature for the first three months of treatment

remained between 98.6° and 100.4° F., between 100.4° and 102.2° F. for the next six weeks while the patient seemed to be improving most, and from this time until his death between 102.2° and 104° F. The author considers that the persistence of the febrile movement and the diminution of the red cells after a number of *x*-ray treatments were more important factors in prognosis than the improvement in the general and local conditions.—*La Semaine médicale*, 1905, No. 46, p. 548.

The Roentgen Rays in Splenic Leukæmia.—ANTON WASSMUTH reports a case of splenic leukæmia which was treated by the *x*-rays and in which improvement, as evidenced by a diminution of the number of leukocytes in the blood and of the splenic tumor, was noted for a time, but which during the treatment developed pernicious anæmia with typical changes in the red blood cells, hemorrhages, a febrile movement, and nervous symptoms. Death finally took place. The author considers that in the *x*-rays we have a means of ameliorating the symptoms of leukæmia, but that the treatment does not strike at the root of the disease. The case is also interesting in that it shows that a lymphatic leukæmia may terminate in a pernicious anæmia.—*Wiener klinisch-therapeutische Wochenschrift*, 1905, No. 46, p. 1151. (Evidently more favorable results can be obtained by the Roentgen rays in this form of leukæmia than by any other method hitherto at our disposal, an opinion that has been confirmed by personal observations, as well as by others which have been reported in this country.—R. W. W.)

PEDIATRICS.

UNDER THE CHARGE OF

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AND

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Venesection in Scarlatinoid Uræmia.—G. SINGER (*Jahrbuch f. Kinderheilkunde*, 1905, Bd. lxii. S. 417) has observed nineteen cases of uræmia in the course of scarlet fever. All were treated by means of venesection; fifteen recovered, four died. In fourteen, nephritis preceded the attack, one had neither albumin nor casts; seven had a diminished amount, four a normal and four an increased amount of urine; twelve had œdema preceding the attack, the other three had no œdema at any time; seven had a slow, tense pulse at the time of the uræmic convulsion, the other eight had a small, frequent pulse, and in them bleeding gave better results than in the others (the only pulse which he considers a contra-indication is the filiform pulse). In nine cases the attack was preceded by an elevation of temperature. In eight of the cases the improvement was immediate, the convulsions disappearing and the consciousness reap-

pearing at once; in two cases improvement was noted in a few hours, consciousness returning twenty-four hours later; in four cases the attacks returned and the venesection had to be repeated (the quantity of blood removed was evidently too small). Of the four patients who died, the causes of death were respectively cardiac weakness, cerebral congestion, and far advanced kidney changes; the last two were admitted in a dying condition. He concludes from his observations that venesection is a rational and beneficial procedure in uræmia in the course of scarlatinal nephritis. The operation is simple and without danger. It is chiefly indicated when cerebral irritation governs the picture; in comatose states the operation may do good, but the chances of improvement are smaller. It is indicated in all types of children, strong, weak and anæmic; it is contraindicated in the presence of a filiform pulse. The sooner venesection is performed, the better the patient's chances. The amount removed should be in proportion to the patient's age, and strength and the virulence of the attack. If not successful, venesection may be repeated after twenty-four to thirty-six hours.

Intussusception in Children.—H. HIRSCHSPRUNG (*Mitteilungen aus den Grenzgebieten*, 1905, Bd. xiv. S. 2) reports concerning one hundred and seven cases of intestinal invagination observed in children at one of the Copenhagen hospitals, between 1871 and 1904. There were seventy-seven boys and thirty girls; the youngest was seven weeks old, the three oldest seven years. All of them were in a good state of nutrition, sixty-one being partly or wholly nursed by their mothers. Points of etiological importance were habitual constipation, intestinal catarrh with frequent loose stools, tumors of the intestines, swelling of Peyer's patches, diffuse hemorrhage into the intestines, and intestinal diverticula. In many of the cases a marked tendency to recur was noted. Of the one hundred and seven patients sixty-five (forty-five boys and nineteen girls; 60.75 per cent.) were cured. Of the forty-six boys, twenty-six were less than a year old, the four youngest being only four months old; eight were between one and two years; seven between two and four years; and six between seven and eight years. Of the nineteen girls cured, nine were less than one year old, the youngest being seventy-six days; the oldest were between three and four years. As regards treatment, Hirschsprung refers all cases in which the small intestine is involved to the surgeon; he treats all large intestine invaginations with narcosis, taxis, and enemata. The differential diagnosis is not easily made; eleven patients with unrecognized intussusception of the small intestine died. The prognosis depends much upon the duration of the affection before admission to the hospital; of fifteen children admitted within eleven hours of the onset, ten died, and of forty-one afflicted for more than twenty-four hours, twenty-two died. He closes with the admonition to operate upon all doubtful cases after a short attempt at taxis.

Dentition.—The view that increase in salivary secretion (stimulation of the salivary glands by irritation transmitted from the gums to the tensor tympani) is a sign of approaching dentition is not shared by T. J. ELTERICH (*Pennsylvania Medical Journal*, 1906, ix., p. 378). He considers it more reasonable to assume that the abundant salivary secretion indicates a stage of developmental activity preparing the digestive organs for the aliment to follow, than to regard it as a mani-

festation of a morbid condition of the salivary glands due to dental irritation. Fever, restlessness, and disturbed sleep are often credited to the approaching eruption of a tooth, when more careful examination will show the existence of other conditions sufficiently adequate to produce these symptoms. Many infants cut their teeth without any disturbance of the general health. As a tooth approaching the surface makes the gums almost white and insensitive, he believes the eruption to be absolutely painless and devoid of deleterious symptoms. The thickening of the gum is due to the advancing of the tooth. He considers stomatitis credited to teething due to unclean nipples, bottles, or thumbs. He believes gastrointestinal derangements credited to teething (occurring usually during the weaning period) due to bacterial invasion, improper food, atmospheric changes, etc. Such disturbances should always be treated even though mild. Middle ear inflammations and meningitis have often been observed to follow mild diarrhœas of these types. Otalgia credited to teething is usually due to a pus infection of the middle ear. Bronchitis should always be considered to be due to the child having been exposed to atmospheric changes, and not to nervous irritation reflected from the gums. As the real causes of convulsions are beginning to be known, convulsions attributed to teething are being thinned out. Acute indigestion and rachitis when searched for will probably explain the greater number of the cases. Many causes for cutaneous eruptions besides that of dentition can be found if carefully searched for.

A New Method of Resuscitation in Asphyxia Neonatorum.—After all other methods failed to resuscitate apparently asphyxiated children, W. HIMMELSBACH (*California State Journal of Medicine*, 1906, iv., p. 42) gave newborn children hypodermic injections of strychnine sulphate 1/1500, grain, and atropine sulphate 1/2000 grain. After a few minutes in almost all cases he was rewarded with an occasional gasp, and after an hour the children were breathing and crying normally.

Antidiphtheritic Serum in Stomatitis and Vulvovaginitis of Infancy.—After discussing the causation and the treatment of the different varieties of stomatitis, E. GIORELLI and A. BRINDA (*Archives de Médecine des Enfants*, 1905, viii., p. 724) report having treated twenty-five patients so afflicted with injections of antidiphtheritic serum and invariably with good results. They were led to employ it first in the case of a four-year-old boy in whom the process continued spreading along the right cheek, gum, and right side of the tongue in spite of the usual applications; the process had existed for ten days. After six injections of 500 units each the patient was on the road to recovery. Many of the patients recovered after one injection of 1000 units; in none were more than 5000 units necessary. Many of the children were studied bacteriologically; in most of them only streptococci and the pneumobacillus of Friedländer were found; in a few a bacillus resembling the Löffler organism. They pursued the same line of treatment in nine cases of ulcerating vulvovaginitis in infants, using from one to five injections in each case. In three of them gonococci were discovered; in the other six bacteriological studies could not be made, but the authors are satisfied that they were not of gonococcal origin. In all nine rapid recovery followed the use of the serum.

OBSTETRICS.

UNDER THE CHARGE OF

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Hæmatology of Pregnancy and the Puerperal Period.—GIVEN (*Journal of Obstetrics of the British Empire*, April, 1906) contributes a paper upon this subject, giving results of the study of the blood in twelve consecutive cases during pregnancy and the puerperal period. The examinations were made about noon each day to avoid the influence of digestion. The first examination in each case was made before labor and further examinations were made twenty-four hours later, after delivery. The red cells were few in number at the end of pregnancy and a further slight diminution occurred immediately after labor; then the number was increased to normal. The leukocytes were increased before labor, being 10,500; within twenty-four hours after labor they rose to between 15,000 and 16,000, and then gradually dropped to 7250 on the twelfth day.

Given concludes from these observations that in the last months of pregnancy there is a slight leukocytosis; probably commencing during labor, there is observed a sudden and well-marked leukocytosis immediately after labor; this is a polymorphonuclear increase and rapidly falls to normal. This change is equally common in primiparæ and multiparæ, and occurs alike at full term or premature labor. When the child dies before labor commences and when there is deficient excretion the change is but slight. It is not influenced by chloroform and other drugs.

There is a well-marked increase in lymphocytes commencing a few days after delivery and being very marked during the second and third weeks. This seems to be connected with involution of the uterus. The more marked this change is the better the patient is doing and the more rapid is her return to health.

Chronic Inversion of the Uterus of Puerperal Origin.—MCLAIN (*Journal of Obstetrics of the British Empire*, April, 1906) reports a case of a multipara who at labor had retained placenta and considerable traction on the cord; this was finally followed by the delivery of the placenta and membranes; hemorrhage persisted and its cause was unrecognized. On examination the uterus was inverted, the mucous membrane soft, and considerable hemorrhage occurred upon slight manipulation. Under deep anæsthesia a volsellum forceps was fixed anteriorly and posteriorly in the middle line at the junction of the cervix and vagina. Pressure applied against these points caused the contraction ring to become evident; four forceps were then applied, when with pressure by the thumbs over the fundus the uterus was gradually replaced. Iodine was applied thoroughly to the cavity, sterile gauze was firmly packed, and a silkworm-gut suture was applied at each angle of the widely opened cervix. The patient made a good recovery.

A Simple Device for Extraction of the Child in Breech Presentation.—WIENSKOWITZ (*Zentralblatt f. Gynäkologie*, 1906, No. 13) has used for some time a strong, red rubber band about two and one-half feet long and one-half inch in width. This can be disinfected by boiling; it is introduced without difficulty, passed over the thighs of the child, and traction made at intervals with the hand. No injury was done to the child by this method and the results were exceedingly satisfactory.

Pregnancy Complicated by Gangrene of the Vulva.—GOTÆ (*Zentralblatt f. Gynäkologie*, 1906, No. 18) reports the case of a patient, aged eighteen years, a multipara, who while lifting a heavy basket bruised the external genitals. Three days afterward swelling occurred with pain on motion, and on examination, redness, swelling, and infiltration were found. This went on to necrosis, and it was necessary to open certain areas with the electrocautery. The patient made a tedious recovery from the gangrenous condition in forty-three days. She was found to be about five weeks pregnant.

GYNECOLOGY.

UNDER THE CHARGE OF

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Relaxation of the Uterus during Curettement.—VAN TUSSENBROCK (*Zentralblatt f. Gynäkologie*, No. 2, 1906) discusses this question at length, aiming at the conclusion that the atony of the uterine muscle sometimes observed during curettement is not due to narcosis, but to direct irritation by the curette. That this atony is of a reflex character is shown by the fact that it is often local, being confined to the cornua or to the anterior wall. Whether this reflex action is of central or peripheral origin is not yet certain.

The writer agrees with other observers that the introduction of laminaria tents may favor uterine relaxation, which is increased by the subsequent curetting.

Observations in Menstruation.—SHAEFFER (*Zentralblatt f. Gynäkologie*, No. 2, 1906) bases his deductions on 10,500 cases. The average age at which menstruation began was 15.7 years, being a little later in the case of girls living in cities. In 85 per cent. menstruation began between the years of thirteen and eighteen.

As regards the menopause the writer states that the great difficulty in collecting prime statistics is due to the frequency of pathological conditions. The average age in 903 cases was 47.26 years, the earliest age being twenty-eight and the latest fifty-seven years.

It was found that in women who menstruate early the menopause is established about one year later than the average.

Metastases in Carcinoma of the Ovary.—In a discussion on this subject before the Dresden Gynecological Society (*Zentralblatt f. Gynäkologie*, No. 2, 1906) WEINDLER denied that metastases occurred in the stomach. Schmarl affirmed that he had found secondary cancer of the ovaries in connection with primary disease of the stomach, breast, lungs, and even the mouth and œsophagus, although no clinical symptoms referable to the pelvis might be present.

Von Holst cited a case in which cancer of the ovary developed a year after supravaginal amputation for uterine fibroid, with secondary deposits in the abdominal viscera. Although there was no evidence of malignant disease at the time of the operation it must have been present.

Early Operation in Appendicitis.—KROGINS (*Deutsche Zeitschift f. Chirurgie*, Band lxxviii., Heft 4 to 6) understands by this operative intervention during the first thirty-six hours. He urges its importance in view of the lower mortality in seven cases, recognizing two types—the perforation characterized by sudden onset and severe pain, and the gangrenous, in which the initial symptoms are not so severe as in the former, but become rapidly worse. The indications for prompt intervention are general muscular rigidity of the abdominal wall, diffuse tenderness on pressure, severe pain, rapid and soft pulse, repeated chills, vomiting, and constipation.

Chorioepithelioma.—LISSAUER (*Zeitschrift f. Krebsforschung*, Band iii., Heft 2) reports a case in which he performed an autopsy upon a patient dying from cancerous disease of the pulmonary artery two years after extirpating the uterus. No other foci were found in the body. That the thrombus had developed slowly was proved by the presence of marked hypertrophy of the right ventricle. The chorium epithelium had evidently developed within the lumen of the vessel and had not extended from without inward.

Globus Hystericus.—BUCH (*St. Petersburger med. Wochenschrift*, Band xxii., No. 4) differs from the other writers who regard globus as a sensation of cramps in the œsophagus, regarding it as purely a sensory phenomenon and not a true œsophagismus of sympathetic origin. Excitation of the lumbar sympathetic plexus is conveyed upward from one set of ganglia to the next above until the sensory centres are involved. The sensation is one of pressure, and when it reaches the throat gives the impression of a foreign body.

The writer denies that the globus is pathognomonic of hysteria, believing that it is merely a symptom of general hyperalgesia of the sympathetic nerves, which may be present in other conditions. He noted only one case of hysteria among twenty in which the globus was present, most of the patients being chlorotic females, who all recovered under the administration of iron or arsenic.

Appendicitis Accompanying Disease of the Adnexa.—ROSE (*Zentralblatt f. Gynäkologie*, No. 4, 1906) found the appendix diseased in thirteen out of 199 cases in which he operated for diseased adnexa. In every instance the appendicular disease was secondary. The writer has never seen a case in which inflammation extended from the appendix to the pelvic organs.

The diagnosis is difficult. In eight cases it was made from the presence of tenderness over McBurney's point. In these an incision was made along the border of the right rectus.

The writer recommends that abdominal section should be preferred to vaginal section whenever an appendicular complication is suspected and that the adherent appendix should always be removed, not simply freed.

Intestinal Autointoxication after Laparotomy.—KELLER (*Zentralblatt f. Gynäkologie*, No. 4, 1906) reports two cases in which fever, rapid pulse, and tympanites developed after operation, with obstinate constipation and indican reaction in the urine. The patients finally became comatose. Only on the fifth day did he succeed in moving the bowels by purgatives and enemata, the stools being foul-smelling. Irregular diarrhœa followed, the symptoms gradually subsided, and the patients subsequently convalesced normally.

The writer advises giving nourishment by the mouth as soon as possible after operation, the avoidance of opium, and early evacuation of the bowels.

Results of Ovariotomy.—FRITSCH (*Zentralblatt f. Gynäkologie*, No. 4, 1906) reports 989 ovariotomies performed in the course of twenty-two years, with a mortality of 7.1 per cent. Only 2.3 per cent. were due to sepsis. In forty-eight out of seventy deaths the tumors were malignant.

The writer calls attention to the great improvement in statistics since Hegar, in 1874, affirmed that the only indication for the removal of a tumor was the symptoms to which it gave rise.

Tuberculous Ovarian Cysts.—In the *Lyon Médical*, February 26, 1906, are reported two cases of ovarian cystoma in which the lining membrane was studded with miliary nodules in one instance and with cheesy masses in the other. No other tuberculous foci were discoverable. Sixteen similar cases have been reported, some of which were doubtful.

In order to establish the authenticity of a case it must be shown, that the cyst is ovarian, that the disease has not extended from a tuberculous salpingitis, and that undoubted tubercles are present. Either the interior or exterior of the cyst may be affected. The disease is in most instances secondary to tuberculous salpingitis or peritonitis, being conveyed by the lymphatics.

OPHTHALMOLOGY.

UNDER THE CHARGE OF

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A Case of Permanent Extensive Changes of Both Maculæ from the Direct Rays of the Sun.—ZIRN (*Graefe's Archiv f. Ophthal.*, lx., 3) reports the case of a weak-minded boy who had looked for some time, on a morning near the end of May, directly at the sun; the next day the lad noticed that his sight was not so good. Examination December 1st: R. vision equalled fingers at 3 metres; L., fingers at 3.5 metres. Jaeger at 22 cm. eccentric fixation, periphery of the field normal, small absolute scotoma nearly central. The ophthalmoscope showed in both eyes in the region of the maculæ oval patches (about one disk diameter vertical by one and one-half horizontal) moderately pigmented and bordered by interrupted strongly pigmented margins. Brilliant stipplings and small yellowish spots could be seen scattered among the patches. The visual acuity finally increased to about double that noted above wih tno change in the fundus.

Rheumatism of the Ocular Muscles.—PICHLER (*Wien. klin. Wochen.*, No. 14, 1905) observed among one hundred and sixty patients with acute rheumatism of the joints four cases of rheumatism of the ocular muscles. There was no formation of nodules, there was uniformly slight swelling, the redness was diffuse not sharply defined, and separated from the cornea by a broad pale zone. The tendons were sensitive to pressure.

Is the Sclera of Myopic Eyeballs Deficient in Elastic Fibres?—ELSCHNIG (*Wien. klin. Rundschau*, No. 29, 1905) finds that Lange's hypothesis that myopia depends upon congenital deficiency of elastic fibres in the sclera is unfounded. His own researches showed that as regards the scleral elastic fibres the myopic eyeballs are exactly like the emmetropic; the sclera of the former presents a decidedly greater degree of thinning in the region of the staphyloma than would simply correspond to a sclera of normal thickness which had undergone thinning in consequence of the stretching and lengthening of the optic axis, and this is the only characteristic of the sclera of a myopic eyeball.

The Sole Prophylaxis against School Myopia.—GRUNNERT (Ophthal. Society of Heidelberg, reviewed in the *Archiv. d'Ophtal.*, Nov. 1905) denies the existence of congenital predisposition to myopia. The best preventive consists in diminishing reading and writing in the primary classes. Exercises in reading and writing should not begin until the

child is eight years old. These statements were contradicted by others present, upon the ground of too rigid formulation. Siegrist insisted upon the role played by astigmatism and opacities of the cornea in the etiology of myopia. Astigmatism being congenital does constitute a congenital predisposition to myopia.

Lange's assertion that congenital predisposition to myopia is due to a relative deficiency of elastic fibres in the sclera is denied by other observers.

Ill Effects of Adrenalin.—BOUCHART (*Revue d'Ophtal.*, May, 1905) has noted the following phenomena after a tenotomy done under a mixture of adrenalin and cocaine: Persistent mydriasis, exudate into the iris localized in the crypt zone with loss of pigment and atrophy, loss of transparency of the cornea with bullæ. The reporter believes that the conditions noted were caused by the adrenalin, for the reason that they greatly resemble the effects of the drug produced experimentally, that the lesions disappeared under remedies causing hyperæmia and myotics, and that the phenomena were most marked in the region nearest the field of operation.

DISEASES OF THE LARYNX AND CONTIGUOUS STRUCTURES.

UNDER THE CHARGE OF
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Roentgen Rays in the Diagnosis of Disease of the Frontal Sinus.—DR. GOLDMANN, of Freiberg, gave a demonstration of the utilization of the Roentgen rays in the region of the frontal sinus (*Elfte Versammlung Suddeutscher Laryngologen*, 1904). The patient lies down with the forehead upon the photographic plate. The exposure varies from one and one-half to two minutes, according to the thickness of the skull and the age of the patient. The frontal sinuses are thoroughly revealed in their frontal aspect. In addition to the frontal, temporal, and orbital bulgings the frontal cells lying under the frontal process of the upper jaw can be recognized, likewise the region of the nasal lacrymal duct, and in favorable cases the maxillary sinuses also.

Successful Tracheotomy and Laryngofissure in a Case of Fibroma of the Larynx and Trachea.—DR. E. VON NAVRATIL reported to the Hungarian Society of Medicine of Buda-Pesth (*Révue hebd. de Laryngologie, d'Otologie et de Rhinologie*, November 11, 1905) a case of fibroma of the larynx and trachea in a man forty-five years of age, who arrived at the hospital in such a suffocating condition that tracheotomy had to be performed immediately. Laryngoscopic examination revealed the larynx entirely filled with a large pale-red tumor. Attempts at endolaryngeal removal were difficult and unsatisfactory, though several pieces were removed. Subsequently, the larynx was opened in the median

line and revealed the presence of two growths, one the size of a walnut, the other smaller. They were cut off at their base close to the intact vocal bands and thyroarytenoid ligaments. Cartilage and skin were both closed with suture. Cicatrization took place by first intention, respiration was promptly re-established, and the voice soon became clear. Histological examination showed it to be soft fibroma.

Disintegration of a Peanut in the Bronchus.—PROFESSOR THOMAS A. CLAYTOR, of Washington, D. C., reports (*Journal of the American Medical Association*, November 11, 1905) a case of foreign body in a bronchus which seems to indicate the spontaneous disintegration of a peanut incarcerated in the right primitive bronchus.

Hemorrhage of the Vocal Band.—A. J. BRADY, of Sydney Hospital, N. S. W. (*Journal of Laryngology, Rhinology and Otology*, November, 1905), reports a case of sudden voicelessness in a professional singer while singing, which was found to be due to a rupture of a small blood-vessel in the submucosa gland, and was attributed to singing music above the normal register.

Foreign Body Removed from the Right Bronchus.—DR. CHAS. A. ELSBERG, of New York, reports (*The Laryngoscope*, December, 1905) the removal from the right bronchus, under bronchoscopy, through a tracheal incision, of a pin one and a half inches in length from a child four years of age. A very ingenious procedure was employed to bend the pin upon itself so that it could be grasped at the bend and be thus readily extracted.

Temporary Injury to Voice during Operation upon the Thyroid Gland.—At a meeting of the California Academy of Medicine, January 20, 1906 (*Journal of the American Medical Association*, March 17, 1906), DR. W. I. TERRY, in a report of nine successful operations upon the thyroid gland under local anæsthesia, mentioned one patient whose voice suddenly became squeaky while the inferior thyroid artery was being tied, when it needed only readjustment of the ligature to free the nerve, which was not itself seen.

Laryngeal Tuberculosis.—An unusual case of laryngeal tuberculosis is reported by DR. OTTO J. STEIN, of Chicago (*The Laryngoscope*, November, 1905). A rugged clothing merchant, fifty years of age, was suddenly seized with acute pain in the right abdomen. A month later the abdomen was opened and a portion of diseased omentum removed. The surgeon considered this omentum tuberculous. Soon afterward hoarseness supervened and in a short time the larynx presented serious ulceration in both vocal bands with other tuberculous manifestations in other portions of the structure. No tubercle bacilli could be found in the secretions, in the expectoration, nor in the debris removed by curetting. Four years ensued before any inflammation of the lungs could be detected, and four months later the patient succumbed. At the autopsy there was no evidence of recurrence in the omentum. The first two or three feet of the small intestine showed several areas of tuberculous infiltration, but without any breaking down of the tissue; the remaining portions of the alimentary canal seeming normal. Both

lungs were peppered throughout with miliary infiltration. There were no abscess cavities nor cicatrices to be found, and only a few calcareous spots. The larynx was very much involved, almost every part having participated in the tuberculous process.

Syphilis of the Upper Air Passages.—In a lecture on "Some Unusual Manifestations of Syphilis in the Upper Air Passages," delivered at the London Polyclinic by SIR FELIX SEMON (*British Medical Journal*, January 13, 1906), the subject was illustrated by the report of four cases. In the first one, a precocious tertiary syphilis of the throat and tongue of malignant type, after failure with the approved methods of the day a cure was effected with Zittmann's decoctions. (The compiler can confirm the value of this old-fashioned and almost neglected treatment in analogous instances.) The other cases reported were respectively: one of tertiary syphilis of the larynx and trachea followed by isolated tertiary syphilis of the rhinopharyngeal cavity; early fibroid infiltration of the pharynx and larynx in a case of obstinate recurring secondary syphilis; and tertiary syphilis of the larynx manifested particularly by periodic inflammation with the production of ephemeral papillomatous excrescences.

Roentgen Ray Illumination in Diseases of Accessory Sinuses.—MOSHER (*The Laryngoscope*, February, 1906) contributes a valuable paper upon the use of the *x*-rays in sinus diseases, with illustrations from radiograms of a number of patients and detailed interpretations thereof. These reproductions are far more distinct than could possibly be procured from any similar plates which the compiler has yet seen.

The Point of Origin of Mucous Polyps in the Posterior Nares.—KILLIAN (*Annales des Maladies de l'Oreille, du Larynx, du Nez et du Pharynx*, Mai, 1906) maintains as a result of his clinical experience and histological investigations that the unilateral and solitary mucous polyp of the posterior nares has its origin in the mucous membrane of the maxillary sinus.

Fatal Pyemia following the Removal of the Posterior End of the Left Inferior Turbinate.—STEIN (*The Laryngoscope*, January, 1906) reports a case of acute bilateral middle ear suppuration following the removal of the posterior end of the left inferior turbinate in a woman, forty-one years of age, and resulting fatally.

Osseous Occlusion of the Nasal Passages.—BOTEY (*Annales des Maladies de l'Oreille, du Larynx, du Nez et du Pharynx*, April, 1906) reports a case of complete congenital osseous occlusion of the entire right nasal fossa. A similar imperfect, but almost complete, atresia existed upon the left side. The patient was a female, aged nineteen years, a subject of hereditary syphilis with hyperostoses of various bones of the face and of both tibias. Entire relief to the nasal respiration was produced by tunnelling the passage through the bone, principally with gouge and mallet. Seven weeks thereafter the patient was well, both nasal fossa being thoroughly permeable.

DERMATOLOGY.

UNDER THE CHARGE OF

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A Case of Systematic Blastomycosis, with Blastomycetes in the Sputum.—EISENDRATH and ORMSBY (*Journal of the American Medical Association*, Oct. 7, 1905) report a new case of systemic blastomycosis. The patient was a Polish laborer, aged thirty-three years, who began to be ill in February, 1904, with a feeling of discomfort in the right side of the chest. Four months later the first cutaneous lesion appeared and was shortly followed by others. Upon his admission to the hospital in February, 1905, he was much emaciated, very weak, and had some elevation of temperature. At this time, variously sized lesions were present on the legs, forearm and face. Pus removed from an unruptured abscess on the left forearm and inoculated upon various media produced pure cultures of blastomycetes. This pus was also examined for tubercle bacilli, with negative results, and injections of tuberculin likewise gave negative results. Although the patient denied having any considerable cough or expectoration, considerable blood-stained, mucopurulent sputum was collected on one occasion in which numerous blastomycetes were found. The apex and upper lobe of the right lung were dull posteriorly and there was practical absence of lung expansion. Under large doses of potassium iodide internally, with radiotherapy and antiseptic dressings locally, improvement occurred, and the patient left the hospital greatly improved. When seen a few weeks later, however, he was found to have relapsed. Guinea-pigs inoculated with pus, sputum, and granulation tissue from an abscess wall produced local, but no general infection.

Black Penis due to Antipyrin.—H. MALHERBE (*Jour. des Mal. Cut. et Syph.*, July, 1904, p. 499) described the case of a man, aged thirty years, accustomed to taking antipyrin for migraine, who after one dose of about 22 grains observed the penis turning black. Aside from the color of the skin the penis was normal. Similar cases have been seen by Fournier, who recorded three cases in 1899. Considerable tonic treatment is usually required for its disappearance. In nature the condition may be compared with the persistent erythematopigmented diseases described by Brocq.

Lupus Erythematosus is not Tuberculous.—O. KREN (*Archiv. f. Derm.*, vol. lxxv. p. 303) arrives at this conclusion: In a patient who at death showed atypical lupus erythematosus, the autopsy gave no proof of tuberculosis of any organ. The theory of the cutaneous disease being the result of toxins of tuberculosis is not borne out by the observations that have been collected.

Origin of Pigment.—EHRMANN, so favorably known for his work on the pigment of the human body, concludes (*Brit. Journ. of Derm.*, October, 1905, p. 385): (1) That melanin is intracellular, and in the situations where it is present occurs in the deeper layers of epidermal cells and in certain mesoblastic cells known as melanoblasts; (2) that melanoblasts are specialized connective-tissue cells, which are round, spindle-shaped, or branching, and are peculiar not only in containing melanin granules, but also in having larger nuclei, which stain more faintly than those of ordinary connective-tissue cells; (3) that melanoblasts occur in the upper layers of the corium, are specially noticeable around the bloodvessels, and are also present as peculiar branching structures in the interepithelial lymphatic spaces of the deeper portion of the epidermis; (4) that melanin is a derivative of blood-pigment, the material from which it is formed getting out of the bloodvessels, into the perivascular tissue-spaces, where it is taken up by the melanoblasts and transformed into melanin; and (5) that the epidermal cells do not elaborate melanin, but absorb it from the melanoblasts in the interepithelial lymphatics.

Diseases of the Skin in Kidney Diseases.—A. JORDAN (*Monatsh. f. pract. Derm.*, vol. xxxix. p. 637) has observed two cases of pruritus and of generalized furunculosis, two cases of eczema, and one of gangrene in subjects who presented a larger or smaller percentage of albumin in the urine; but neither these observations nor other rare cases published are sufficient to warrant the creation of a special group of albuminic dermatoses. It, nevertheless, must be admitted without question that there exist some diseases of the skin which have a direct connection with the renal function, and to these Thiebierge in particular, directed special attention in 1885.

Mercury in Syphilis.—OTTO LERCH (*American Medicine*, November 4, 1905) explains why mercury is more effective when given by inunction than other methods. By inunction it is absorbed by the lymphatics and comes in direct and immediate contact with the virus. Enlarged glands will yield to inunction after resisting every other treatment. Lesions of the bloodvessels, viscera, bones, and the nervous system follow the lymphadenitis. Enlarged glands are found early in the disease and they may be palpated when every other symptom has disappeared. They contain the virus, and a late secondary infection may be explained as originating from them when the resisting power of the organism is lowered. Deep-seated glands cannot be inspected, and it is, therefore, impossible to say when a patient is cured. Antiluetic treatment should be tried in tabes and paresis, as it is often impossible to make a positive diagnosis. A certain analogy between syphilis and tuberculosis has led him to give inunctions of iodoform in tuberculosis, and with good results.

PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF

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The Influenza Bacillus and its Role as a Cause of Disease.—JOCHMANN (*Deut. Arch. f. klin. Med.*, 1905, Bd. lxxxiv. p. 470) presents his views, which are based on much personal investigation, upon the role that the influenza bacillus plays in the production of disease.

In working with the organism he finds that, in spite of statements to the contrary, hæmoglobin is always necessary in culture media for its growth. He confirms the work of others in regard to the growth of the organism in symbiosis with the staphylococcus, gonococcus, and xerosis bacillus, and finds that the presence of the pneumococcus and streptococcus also favor the growth of the bacillus.

The author investigated the blood of all his cases in which the sputum showed the organism, but was never able to obtain influenza bacilli from this source, and he considers the invasion of the blood by the influenza bacillus very rare in spite of the numerous positive findings of Jehle and others, whom he believes were dealing with agonal or post-mortem infections.

A thorough study of the occurrence of the organism in the diseases of childhood, as measles, diphtheria, scarlet fever, and whooping-cough, was made. He frequently found the organism in the first three diseases present as a saprophyte, and without having any apparent influence on the course of the disease, and its presence is not sufficient evidence to consider the original disease complicated by influenza. All of these diseases, however, showed not infrequently catarrhal bronchitis and lobular pneumonia, from which the organism could be obtained in great numbers. Jochmann considers that these complications are due to the influenza bacillus.

In whooping-cough a bacillus, morphologically and culturally identical with Pfeiffer's bacillus, was so constantly found in the sputum, that the author considers it proved as the cause of whooping-cough, as much as it is proved to be the cause of influenza.

The presence of the organism has been shown in tuberculous and bronchiectatic cavities of the lungs, where it may exist without influencing the course of the pre-existing disease, although in pandemics the influenza bacillus may give rise to a terminal infection in tuberculosis.

The author is opposed to recognizing chronic influenza upon bacteriological findings alone.

Jochmann's recent experience with endemic influenza has shown him that the bacillus is present in certain cases only in small numbers or seems to be absent, while other pathogenic organisms may be pre-

sent in large numbers. This has led him to hold, that, although the bacillus of Pfeiffer is the cause of epidemic influenza, other organisms, especially the pneumococcus, streptococcus, and perhaps the micrococcus catarrhalis, must be considered accountable for endemic cases when a symptom-complex similar to the epidemic form is seen. He suggests that grippe be the name given to the cases caused by these other organisms, and influenza be reserved for the symptom-complex together with the isolation of the influenza bacillus in large numbers. He considers bacteriological findings alone insufficient evidence upon which to make the diagnosis of influenza.

Hamartoma (Tumor-like Malformations) of Kidney and Liver.—At the suggestion of Albrecht, GENEWEIN (*Zeit. f. Heilk.*, 1905, Bd. xxvi. p. 430) has studied the small, circumscribed fibrous nodules found so often in the medulla of the kidney, and frequently in the liver, to determine their exact relationship to true tumors. He finds on microscopic examination that the nodules from the kidney, so well circumscribed microscopically, have ill-defined borders, and that their margins run imperceptibly into normal kidney substance. They are formed of regularly arranged connective-tissue fibres, continuous with the connective tissue of the surrounding structures, and contain normal or almost normal kidney tubules, which are probably the descending loops of Henle. These nodules are distinctly different from tumors as defined by Borst and others, in that they are composed of elements differing in no respect from the normal structure of the organs in which they are found, and show no new-formation of their elements. The only difference from the surrounding medulla seems to be in the increase of the connective tissue about and between the tubules. The author believes that they are tumor-like malformations of fetal origin, and suggests for them the name of "hamartoma fibrocanabiculare." Analogous structures were found in the liver. Here the connective tissue was pierced by bile canaliculi. The type of structure and mode of origin were considered to be the same as for the nodules in the kidney.

A Specific Serum for Trypanosoma Brucei and its Action upon Trypanosoma Gambiense.—KLEINE and MOLLERS (*Zeit. f. Hygiene und Infekt.*, 1906, Band lii. p. 229) inoculated asses with the serum of rats inoculated with Trypanosoma brucei. It was impossible to use the blood of rats, for this produced grave constitutional disturbances in the asses owing to the resulting hæmolysis. By centrifugalizing the defibrinated blood of the rats a clear serum could be obtained containing enormous numbers of trypanosomes. 30 c.c. of serum was given at a dose and four doses were given at fourteen-day intervals. After the second dose the serum of the ass showed protective substance against trypanosoma infection in mice, which the normal serum did not contain; 0.5 c.c. of serum protected mice and prevented the appearance of trypanosomes in the blood against doses of 0.2 c.c. of trypanosoma laden blood injected intraperitoneally, while control mice died in five to six days. The serum had no curative properties, though it delayed the death of the animals. Much the same results were obtained if guinea-pigs instead of mice were used. Against infections by Trypanosoma gambiense there was no specific action, though repeated doses of the T. brucei serum retarded definitely the appearance and devel-

opment of T. gambiense in the blood of infected mice. The asses that furnished this serum did not develop an active immunity, but, on the other hand, emaciated and died. Microscopic examination of the blood failed to show trypanosomes, but if large quantities of serum (20 c.c.) were injected into dogs, the dogs developed trypanosomiasis, from which they died. The authors believe that in the ass the trypanosomes acquire an immunity against the serum.

Working with brilliant green, Wendelstadt and Fellmer (*ibid.*, p. 263) have discovered that this substance has much the same effect upon the trypanosomes in infected animals as was shown to exist for trypanroth by Shiga and Ehrlich. Injections of brilliant green in rats and apes whose blood is swarming with nagano trypanosomes causes a disappearance of the organisms from the blood and prolongs the life of the animals. A combination with arsenic increases the action and often brings about a cure. For a certain time after the injections of brilliant green the blood of the treated animal is not infectious. As the trypanosomes are destroyed in the blood curious forms of the organism are found which have a cystic appearance. They are found principally in the spleen. The author believes it possible that these forms may have something to do with the life cycle of the organism.

HYGIENE AND PUBLIC HEALTH.

UNDER THE CHARGE OF

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Preservation of Milk.—BEHRING, who advocates the treatment of milk for infants with formalin, has asserted that the presence of one part of the preservative in 4000 parts of milk makes no appreciable difference in the taste of the milk, which statement is denied by DR. LEO SCHAPS (*Zeitschrift für Hygiene und Infektionskrankheiten*, Bd. l. p. 247), who finds that in the proportion of 1 in 10,000 it causes an objectionable taste, which is perceptible when the proportion is as small as 1 in 40,000. While formalin checks the development of the lactic acid bacteria, its action upon staphylococci intentionally introduced was found to be far less marked, even when the proportion was raised to 1 in 5000, which strength was found to be not effective against tubercle bacilli placed in both raw and cooked milk. Behring's statements are controverted also by PAUL SOMMERFELD (*ibid.*, p. 153), who found that while formalin in the proportion of 1 to 5000 or 1 to 10,000 has a marked inhibitory influence on milk bacteria when the milk is kept at 50° to 60°, it has hardly any influence in diminishing their number after twenty-four hours, when the milk is kept at 68° and above. When the treated milk was kept at ordinary incubator temperature it yielded about the same number of bacteria per cubic centimetre as the control specimens. Pathogenic bacteria (typhoid and diphtheria) added to

sterilized milk were found to resist the influence of formalin, 1 to 5000, when the milk was kept at room temperature for twenty-four hours, and at incubator temperature for forty-eight hours.

Budde has proposed as a proper, efficient, and harmless method of sterilizing milk the addition of small amounts of hydrogen peroxide and warming to 104°. P. GORDAN's (*Centralblatt für Bakteriologie*, etc., Nos. 22, 23, Abth. 2, Bd. xiii.) experiments show that the amounts recommended by Budde exert no appreciable influence. Larger amounts exert a marked inhibitory influence upon the lactic acid bacteria, but not infrequently streptococci and peptonizing bacteria are hardly affected. Only when three times as much as Budde advised is used, equal to 1.05 per cent. of Merck's preparation, are all the bacteria killed; but the disagreeable taste that it imparts makes its use impossible. M. LUKIN (*ibid.*, Bd. xv., No. 7) attributes the various adverse reports on the method to the use of the ordinary commercial preparations instead of the neutralized form. While he finds Budde's process effective, he agrees that the agent imparts a disagreeable taste which cannot be got rid of. E. BAUMANN (*Münchener medizinische Wochenschrift*, No. 23, Bd. lii. p. 1083) found that while the addition of hydrogen peroxide to the extent of 0.35 to 2 parts in 1000 greatly reduced the number of bacteria in ordinary market milk kept at 113° to 122° for two to three hours, in no case was complete sterility produced; but milk produced under the strictest sanitary conditions and similarly treated was found to be completely sterilized. Sterilized milk inoculated with the organisms of typhoid fever, dysentery, cholera, and tuberculosis, and treated with the agent in the proportion of 0.35 in 1000, and heated as above, remained sterile.

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